Antipsychotics
Therapeutic Class Review (TCR)

April 26, 2019

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCREditor@magellanhealth.com.

FDA-APPROVED INDICATIONS

Indications are for adults unless additional ages are specified.

Drug	Manufacturer	Other Indications	Schizophrenia	Psychotic Disorders	Bipolar Disorder (acute manic episodes)
First Generation Antipsychotics – Oral					
amitriptyline/ perphenazine[1]	Mylan	Moderate to severe anxiety and/or agitation and depressed mood; depressed patients in whom anxiety and/or agitation are severe; depression and anxiety in association with chronic physical disease	--	--	--
chlorpromazine[2]	generic	Acute intermittent porphyria; intractable hiccups; presurgical apprehension and/or restlessness (ages ≥ 6 months); N/V (ages ≥ 6 months); tetanus (adjunct); severe behavioral problems in children (ages 1 to 12 years); short-term treatment of hyperactive children with accompanying conduct disorder (ages 1 to 12 years)	X	X	X
fluphenazine[3]	generic	--	--	X	--
haloperidol[4]	generic	Severe behavior problems in children with combative, explosive hyperexcitability following prior therapy failure (ages 3 to 12 years); short-term treatment of hyperactive children with accompanying conduct disorder following prior therapy failure (ages 3 to 12 years); tics and vocal utterances associated with Tourette's disorder (ages ≥ 3 years)	--	X (ages ≥ 3 years)	--
loxapine[5]	generic	--	X	--	--
molindone[6]	Epic	--	X (ages ≥ 12 years)	--	--
perphenazine[7]	generic	N/V (ages ≥ 12 years)	X (ages ≥ 12 years)	--	--
pimozide (Orap®)[8]	generic, Teva*	Motor and phonic tics associated with Tourette's disorder (second-line; ages ≥ 2 years)	--	--	--

N/V = nausea/vomiting

* Based on a business decision, Teva will discontinue both strengths of Orap tablets (1 mg, 2 mg); generics are available.

FDA-Approved Indications (continued)

Drug	Manufacturer	Other Indications	Schizophrenia	Psychotic Disorders	Bipolar Disorder (acute manic episodes)
First Generation Antipsychotics – Oral *(continued)*					
thioridazine[9,10]	generic	--	X (second-line; pediatrics†)	--	--
thiothixene[11]	Mylan	--	X (ages ≥ 12 years)	--	--
trifluoperazine[12]	generic	Non-psychotic anxiety (second-line; up to 12 weeks)	X (ages ≥ 6 years)	--	--
First Generation Antipsychotics – Inhaled					
loxapine inhalation powder (Adasuve®)[13]	Galen	Acute agitation associated with bipolar I	X (acute agitation associated with schizophrenia)	--	--
First Generation Antipsychotics – Short Acting Injectable					
chlorpromazine hydrochloride[14]	generic	Acute intermittent porphyria; intractable hiccups; presurgical apprehension (ages ≥ 6 months); N/V (ages ≥ 6 months); tetanus (adjunct; ages ≥ 6 months); short-term treatment of hyperactivity in children with conduct disorder (ages 1 to 12 years); severe behavioral problems in children (ages 1 to 12 years)	X	--	X (mania)
fluphenazine hydrochloride[15]	generic	--	--	X	--
haloperidol lactate (Haldol®)[16]	generic	Tics and vocal utterances of Tourette's disorder	X	--	--

N/V = nausea/vomiting

† Pediatric age limit is not specified in thioridazine prescribing information.

FDA-Approved Indications (continued)

Drug	Manufacturer	Other Indications	Schizophrenia	Psychotic Disorders	Bipolar Disorder (acute manic episodes)
First Generation Antipsychotics – Long Acting Injectable					
fluphenazine decanoate[17]	generic	--	X	--	--
haloperidol decanoate (Haldol® Decanoate)[18]	generic	--	X	--	--

N/V = nausea/vomiting

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder			
				Acute Manic Episodes	Depressive Episodes	Acute Mixed Episodes	Maintenance
Second Generation Antipsychotics – Oral							
aripiprazole (Abilify®)[19]	generic, Otsuka	Major depressive disorder (adjunct); Irritability associated with autistic disorder (ages 6 to 17 years); Tourette's disorder (ages 6 to 18 years)	X (ages ≥ 13 years)	X (ages ≥ 10 years for acute treatment as monotherapy and in combination with lithium or valproate)	--	X (ages ≥ 10 years for acute treatment as monotherapy and in combination with lithium or valproate)	X (monotherapy and in combination with lithium or valproate for ages ≥ 10 years)
aripiprazole (with sensor)‡ (Abilify Mycite®)[20]	Otsuka	Major depressive disorder (adjunct)	X	X (acute treatment as monotherapy and in combination with lithium or valproate)	--	X (acute treatment as monotherapy and in combination with lithium or valproate)	X (monotherapy and in combination with lithium or valproate)

‡ Abilify Mycite is a drug-device combination product of aripiprazole tablets embedded with an ingestible event marker (IEM) sensor intended to track drug ingestion approved for use in adults only. Limitations of use include that its ability to improve patient compliance or modify dosage has not been established and that it should not be used in "real-time" or emergency situations to track ingestion as detection may not occur or may be delayed.

FDA-Approved Indications (continued)

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder			
				Acute Manic Episodes	Depressive Episodes	Acute Mixed Episodes	Maintenance
Second Generation Antipsychotics – Oral *(continued)*							
asenapine (Saphris®)[21]	Forest/Allergan	--	X	X (ages ≥ 10 years for acute treatment as monotherapy; adults in combination with lithium or valproate)	--	X (ages ≥ 10 years for acute treatment as monotherapy; adults in combination with lithium or valproate)	X (monotherapy; adults only)
brexpiprazole (Rexulti®)[22]	Otsuka	Major depressive disorder (adjunct)	X	--	--	--	--
cariprazine (Vraylar®)[23]	Allergan	--	X	X (acute treatment)	--	X (acute treatment)	--
clozapine (Clozaril®)[24]	generic, Novartis/HLS	--	X (treatment-resistant schizophrenia; reducing suicidal behavior in schizophrenia or schizoaffective disorder	--	--	--	--
clozapine (Fazaclo®)[25]	generic, Jazz						
clozapine (Versacloz®)[26]	Jazz/Trupharma						
iloperidone§ (Fanapt®)[27]	Vanda	--	X	--	--	--	--
lurasidone (Latuda®)[28]	Sunovion	--	X (ages ≥ 13 years)	--	X (ages ≥ 10 years as monotherapy and in adults in combination with lithium or valproate)	--	--

§ When choosing treatments for schizophrenia, prescribers should consider the ability of iloperidone (Fanapt) to prolong the QT interval and the use of other agents first. Originally, this product was marketed by Novartis via an agreement with Vanda; however, that was discontinued and Vanda is now marketing the product.

FDA-Approved Indications (continued)

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder			
				Acute Manic Episodes	Depressive Episodes	Acute Mixed Episodes	Maintenance
Second Generation Antipsychotics – Oral *(continued)*							
olanzapine (Zyprexa®)[29]	generic, Eli Lilly	Treatment-resistant depression (in combination with fluoxetine)	X (ages ≥ 13 years; second-line in adolescents due to metabolic effects)	X (ages ≥ 13 years as monotherapy and in combination with lithium or valproate; second-line in adolescents due to metabolic effects)	X (ages ≥ 10 years; in combination with fluoxetine)	X (ages ≥ 13 years as monotherapy and in combination with lithium or valproate; second-line in adolescents due to metabolic effects)	X (ages ≥ 13 years)
olanzapine/ fluoxetine (Symbyax®)[30]	generic, Eli Lilly	Treatment-resistant depression	--	--	X (ages ≥ 10 years for acute episodes)	--	--
paliperidone ER (Invega®)[31]	generic, Janssen	Schizoaffective disorder (monotherapy or adjunct with mood stabilizers and/or antidepressants)	X (ages ≥ 12 years)	--	--	--	--
pimavanserin (Nuplazid®)[32]	Acadia	Hallucinations and delusions associated with Parkinson's disease (PD) psychosis	--	--	--	--	--
quetiapine (Seroquel®)[33]	generic, AstraZeneca	--	X (ages ≥ 13 years)	X (ages ≥ 10 years as monotherapy; adults in combination with lithium or valproate)	X	--	X (in combination with lithium or divalproex)

FDA-Approved Indications (continued)

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder			
				Acute Manic Episodes	Depressive Episodes	Acute Mixed Episodes	Maintenance
Second Generation Antipsychotics – Oral *(continued)*							
quetiapine ER (Seroquel XR®)[34]	generic, AstraZeneca	Major depressive disorder (adjunct)	X (ages ≥ 13 years)	X (ages ≥ 10 years as monotherapy; adults in combination with lithium or valproate)	X	X (ages ≥ 10 years as monotherapy; adults in combination with lithium or valproate)	X (in combination with lithium or divalproex)
risperidone (Risperdal®)[35]	generic, Janssen	Irritability associated with autistic disorder (ages 5-17 years)	X (ages ≥ 13years)	X (ages ≥ 10 years as monotherapy; adults in combination with lithium or valproate)	--	X (ages ≥ 10 years as monotherapy; adults in combination with lithium or valproate)	--
ziprasidone (Geodon®)[36]	generic, Pfizer	--	X	X (acute episodes)	--	X (acute episodes)	X (in combination with lithium or divalproex)

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder
Second Generation Antipsychotics – Short Acting Injectable				
olanzapine (Zyprexa®)[37]	generic, Eli Lilly	Acute agitation associated with schizophrenia or bipolar mania	--	--
ziprasidone (Geodon®)[38]	Pfizer	--	X (acute agitation)	--

FDA-Approved Indications (continued)

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder
Second Generation Antipsychotics – Long Acting Injectable				
aripiprazole ER (Abilify Maintena®)[39]	Otsuka	--	X	X (maintenance treatment as monotherapy)
aripiprazole lauroxil ER (Aristada®)[40]	Alkermes	--	X	--
aripiprazole lauroxil ER (Aristada Initio®)[41]	Alkermes	--	X (for initial dose or select missed doses only)	--
olanzapine (Zyprexa® Relprevv)[42]	Eli Lilly	--	X	--
paliperidone palmitate (Invega Sustenna®)[43]	Janssen	Schizoaffective disorder (monotherapy and as an adjunct to mood stabilizers or antidepressants)	X	--
paliperidone palmitate (Invega Trinza®)[44]	Janssen	--	X (treatment in patients after they have been adequately treated with Invega Sustenna for ≥ 4 months)	--
risperidone ER microspheres (Risperdal Consta®)[45]	Janssen	--	X	X (maintenance treatment as monotherapy or in combination with lithium or valproate)
risperidone ER suspension[ll] (Perseris™)[46]	Indivior	--	X	--

Perseris (risperidone ER) was approved as a New Drug Application (NDA) via the 505(b)(2) pathway. A 505(b)(2) NDA is an Food and Drug Administration (FDA) approval pathway in which at least some of the information required for approval comes from studies not conducted by or for the applicant.[47,48]

OVERVIEW

Schizophrenia

The most common psychotic illness is schizophrenia, which affects 1% of the population. Between 25% and 50% of schizophrenic patients attempt suicide, and 10% of patients succeed in their attempt.[49] The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for the diagnosis of schizophrenia includes first ruling out other disorders, and then assessing whether the disturbance has lasted for at least 6 months and includes at least 1 month of 2 or more characteristic symptoms.[50] These symptoms include delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, and negative symptoms, and at least 1 of these should be delusions, hallucinations, or disorganized speech. Symptoms of schizophrenia can be subcategorized as positive, negative, cognitive, aggressive/hostile, and depressive/anxious.

Since schizophrenia is a chronic illness that afflicts all aspects of life, the goals of treatment, according to the 2004 American Psychiatric Association (APA) guidelines, are to stabilize the patient and reduce or eliminate the symptoms, improve quality of life and adaptive functioning, and reduce the likelihood of relapse.[51] Antipsychotics are the standard drugs used in patients with schizophrenia to achieve these goals. This guideline recommends a second generation antipsychotic (SGA) as first-line therapy due to the decreased risk of extrapyramidal symptoms (EPS) and tardive dyskinesia (TD), with first generation antipsychotics (FGA) suggested as appropriate first-line options for some patients. The 2009 Guideline Watch from the APA modifies this recommendation to state that FGAs may be equally effective as second generation agents. This statement is based on studies that have been published since 2002.[52] Notably, as these guidelines are more than 5 years old, the APA does not consider them current; however, they have not published updates or revisions.

The American Academy of Child and Adolescent Psychiatry (AACAP) recommends antipsychotic medication as primary treatment for schizophrenia spectrum disorders in children and adolescents.[53] They further note that safety and effectiveness data as well as comparative data are limited. The AACAP recommends against the use of clozapine as a first-line agent (should be reserved for treatment-resistant patients), state that ziprasidone has not demonstrated efficacy in this population and is not FDA indicated for this population, and caution on its use with olanzapine due to weight gain. Ultimately, the AACAP states that the choice of agent is based on the product's relative potency, adverse effect profile, patient history or medication response, patient and family preferences, provider comfort and/or familiarity, and cost. As this practice parameter is more than 5 years old, it is considered an AACAP historical practice parameter; however, newer guidance is not available.

Bipolar Disorder

Lifelong prevalence estimates of bipolar disorder range from 0.9% to 2.1% of the population.[54] Some of this higher variance is due to subsyndromal forms of the illness included in some estimates. Bipolar disorder is characterized by episodes of mania, depression, or a mixed state. Criterion used to diagnose bipolar I disorder is the presence of a manic episode (persistent elevated, expansive, or irritable mood for at least 1 week with increased energy/activity) or a mixed features specifier (rapidly alternating polarity of mood, sadness, irritability, and mania for at least 1 week), and 3 or more other characteristic symptoms.[55] These symptoms include inflated self-esteem or grandiosity, decreased need for sleep, more talkative than usual or pressured speech, flight of ideas or feelings of racing

thoughts, distractibility, increase in goal-directed activity or psychomotor agitation, and excessive involvement in risky, pleasurable activities. The hallmark of a true manic episode results in symptoms severe enough to cause significant impairment in functioning, requires hospitalization to prevent harm to self or others, or includes the presence of psychotic features.

Criterion used to diagnose a bipolar II disorder includes 1 or more depressive episodes nearly every day during the same 2-week period with at least 1 hypomanic episode lasting at least 4 days. The depressive episodes are marked by the appearance of 5 or more depressed symptoms, which include a depressed mood most of the day every day, diminished interest in activities and hobbies, significant weight change, insomnia or hypersomnia, psychomotor agitation or retardation nearly every day, fatigue, feeling of guilt or worthlessness, indecisiveness or inability to concentrate, and recurrent thoughts of death or suicide. Hypomanic episodes are defined as a persistently elevated, expansive, or irritable mood with increased energy/activity and 3 or more other symptoms. These symptoms include inflated self-esteem, decreased need for sleep, pressured speech, distractibility, increase in goal-directed behavior, and excessive involvement with risky activities. The diagnosis of hypomania is very similar to mania, but the episodes do not result in significant impairment of functioning; they do not necessitate hospitalization and no psychotic symptoms are present.

There is no cure for bipolar disorder, but the appropriate pharmacological treatment can decrease morbidity and mortality associated with the disorder. According to the 2002 APA guidelines, first-line pharmacological treatment for more severe manic or mixed episodes requires the initiation of lithium or valproate plus an antipsychotic agent. SGAs are preferred over the FGAs due to their more tolerable adverse effect profile.[56] As noted in the 2009 Guideline Watch supplement to the APA guidelines for schizophrenia, however, there have been many comparisons between first and second generation antipsychotics since 2002. For a bipolar manic episode with less severity, monotherapy with lithium, valproate, or an antipsychotic may be sufficient. Use of standard antidepressants as monotherapy can precipitate a manic episode in bipolar patients. Use of antidepressants in bipolar patients, misdiagnosed as having non-bipolar depression, can precipitate the first manic episode. During maintenance treatment, recommendations suggest to first optimize the medication dose in patients with bipolar disorder, especially in patients experiencing a breakthrough manic episode, and then consider adding another first-line agent if dose optimization of the initial agent does not lead to a satisfactory response. Another option is to change antipsychotic agents and monitor the patient for response. A Guideline Watch supplement was published in 2005 and included additional data on the use of SGAs (e.g., aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) as monotherapy or adjunctive therapy and an extended-release formulation of carbamazepine for the acute treatment of manic or mixed episodes and stated that these provide clinicians with additional treatment options.[57]

The first-line treatment, according to the 2002 APA guidelines for a bipolar depressive disorder, includes treatment initiation with lithium or lamotrigine; antidepressant monotherapy is not recommended.[58] An alternative treatment option for more severe depressive episodes is the initiation of lithium with an antidepressant. Finally, if an acute depressive episode does not respond to the optimal dose of first-line medication treatment, then the addition of lamotrigine, bupropion, or paroxetine is recommended. Patients with bipolar depression experiencing psychotic features usually require adjunctive treatment with an antipsychotic. The 2005 Guideline Watch states that olanzapine/fluoxetine (Symbyax) and quetiapine (Seroquel) may also be effective for depressive episodes.[59]

Following remission of an acute episode, patients may remain at particularly high risk of relapse for a period of up to 6 months.[60,61] This phase of treatment is considered in the APA guideline as part of the maintenance phase. The medications with the best empirical evidence to support their use in maintenance treatment include lithium and valproate; possible alternatives include lamotrigine, carbamazepine, or oxcarbazepine. If 1 of these medications was used to achieve remission from the most recent depressive or manic episode, it generally should be continued. For patients treated with an antipsychotic medication during the preceding acute episode, the need for ongoing antipsychotic treatment should be reassessed. Varying levels of evidence exist for maintenance treatment of bipolar disorder. Again, as these guidelines are more than 5 years old, the APA does not consider them current; however, they have not published updates or revisions.

Schizoaffective Disorder

Schizoaffective disorder is characterized primarily by symptoms of schizophrenia, such as hallucinations or delusions, and symptoms of a mood disorder, such as mania and depression.[62] Patients also exhibit disorganized thinking, depressed mood and/or manic behavior. Patients with this condition are grouped into 1 of 2 types: bipolar type and depressive type. Treatment and management of schizoaffective disorder includes psychotherapy, such as cognitive behavioral therapy, and pharmacotherapy including antipsychotics, mood stabilizers, and antidepressants.

Depression

National epidemiological data among adults reported that the prevalence of 12-month and lifetime major depressive disorder (MDD), based on (DSM-5) criteria, is approximately 17.3 million American adults or 7.1% of the United States (US) population.[63] The US Preventive Services Task Force (USPSTF) recommends screening for MDD in adolescents ages 12 years and older and in adults.[64,65] This should be supplemented with precautions to ensure accurate diagnosis as well as appropriate treatment and follow-up. The evidence for screening in patients younger than 12 years is insufficient to make a recommendation.

According to the APA's 2010 guidelines, for patients who exhibit psychotic symptoms during an episode of MDD, treatment should include a combination of antipsychotic and antidepressant medications or electroconvulsive therapy (ECT).[66] SGA medications may increase the rates of response or remission of depressive symptoms in patients who typically have not responded to more than 2 antidepressants, even when psychotic symptoms are not present. Generally, in clinical practice, lower doses are used for antidepressant augmentation than for treatment of psychosis. The APA does not consider these guidelines current based on publication date, but new updates or revisions have not been published.

In 2016, the American College of Physicians (ACP) issued guidelines on the nonpharmacologic and pharmacologic treatment of adult patients with MDD.[67] After a review of the literature, they found that cognitive behavioral therapy (CBT) and second generation antidepressants are similarly effective and have similar discontinuation rates. ACP recommends treatment with either CBT or second generation antidepressants for MDD after discussing treatment effects, adverse effects, preferences, and accessibility with the patient. No clinical conclusions were made regarding the efficacy of SGAs.

Autism

Autism spectrum disorder (ASD) is 1 of the most common development disabilities in children in the US.[68] Overall estimates of prevalence vary widely, but most recently was approximated at 16.8 per 1,000 children aged 8 years. The Centers for Disease Control and Prevention (CDC) reported a recent rise in autism over the past few decades. Two key criteria for the diagnosis of autistic disorder in the DSM-5 include impairments in social communication (verbal and nonverbal) and social interaction, and a restrictive, repetitive range of interests, activities, and behavior.

Many medications that have been used for the treatment of autism are not indicated for the disorder; however, oral formulations of aripiprazole (Abilify) and risperidone (Risperdal) are FDA-approved for the treatment of irritability associated with autism in children.[69] The AACAP recommends pharmacotherapy only when there is a specific symptom(s) targeted, but they do not specify the use of 1 antipsychotic agent over another.[70] Similarly, guidelines from the American Academy of Pediatrics (AAP) have been published and do not specify the use of 1 antipsychotic agent over another.[71] The AAP states that given the risks and benefits of atypical antipsychotics (e.g., aripiprazole, risperidone), these agents should only be used to treat severe irritability and problem behavior (I/PB) in ASD only in the following situations: (1) safety is an issue; (2) the behaviors interfere severely with current functioning (e.g., a change in school or residential placement would be necessary otherwise); (3) other interventions have failed or resulted in incomplete improvement; (4) the behavior is unrelated to psychosocial stressors, communication difficulties, underlying medical or psychiatric conditions, or environmental factors; or (5) lower-risk interventions cannot be implemented.

Tourette's Disorder

The prevalence of Tourette's disorder is unknown, but observational studies have suggested a prevalence of 1% in school-aged children.[72] Tourette's disorder is a genetic tic disorder characterized by motor and vocal tics.[73] Generally, individuals have repetitive, stereotyped movements of vocalizations (e.g., sniffing, muscle tension, blinking). DSM-5 criteria for Tourette's disorder state multiple motor and at least 1 vocal tics are present during the illness (not necessarily simultaneously) and have been present for ≥ 1 year, although they may wax and wane in frequency. Onset of these symptoms must occur prior to 18 years of age to be considered Tourette's disorder. Peak tic severity typically occurs between the ages of 10 and 12 years.[74] Tics usually improve during adolescence, with 18% of those older than 16 years experiencing no tics and 60% having minimal or mild tics 6 years after initial examination.

According to the American Academy of Neurology 2019 practice guidelines on the treatment of tics in people with Tourette syndrome and chronic tic disorders, no evidence exists demonstrating that treatment is more effective the earlier it is started and watchful waiting is reasonable, especially in those without tic-related functional impairment (Level B).[75] Comprehensive behavioral intervention for tics (CBIT) may be considered as initial therapy in patients who are motivated to attempt treatment (Level C). Patients should be assessed for comorbid conditions such as attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety disorders, oppositional defiant disorder, and mood disorders (Levels A and B); comorbid mood disorders appear more common in adolescents and adults than children and in those with greater tic severity. Alpha-2 adrenergic agonists (e.g., clonidine, guanfacine) may reduce tic severity, particularly in patients with ADHD (Level B). Regarding other specific pharmacologic agents, haloperidol, risperidone, aripiprazole, and

onabotulinum toxin A (Botox®) are probably more likely than placebo to reduce tic severity. Pimozide, ziprasidone, topiramate, and metoclopramide are possibly more likely than placebo to reduce tic severity. Overall, however, there is insufficient evidence to determine the relative efficacy of these drugs. Notably, a higher risk of drug-induced movement disorders is associated with haloperidol, pimozide, and risperidone and with long-term use of metoclopramide. Patients with severe Tourette syndrome resistant to medical and behavioral therapy may benefit from deep brain stimulation (DBS) via a multidisciplinary approach.

Practice parameters from the AACAP recommend the use of medications for chronic tic disorders in patients with moderate to severe tics causing severe impairment on quality of life or when medication to treat a psychiatric comorbid condition may also benefit the tic disorder symptoms.[76] They do not recommend the use of 1 specific antipsychotic over another, but the AACAP does state that a careful risk benefit assessment should be considered, particularly with the adverse effects of these agents. As this practice parameter is more than 5 years old, it is considered an AACAP historical practice parameter; however, newer guidance is not available. The only SGA FDA-approved for Tourette's disorder is aripiprazole.[77]

Parkinson's Disease (PD)

There is an estimated 1 million people living with PD in the US, with about 60,000 new cases diagnosed each year.[78] Parkinson's disease (PD) is a progressive, neurodegenerative disorder with cardinal motor features of tremor, bradykinesia, and rigidity.[79] This incidence increases significantly with age.[80] Approximately 20% to 30% of patients with PD experience hallucinations and up to 8% experience delusions in advanced stages of the disease.[81]

Atypical antipsychotics have been used to treat hallucination and delusions associated with PD psychosis; however, in patients with only mild hallucinations, antipsychotic treatment may not be necessary. In their 2006 guidelines, the American Academy of Neurology (AAN) recommends that clinicians consider clozapine for patients with PD and psychosis (Level B); the absolute neutrophil count must be monitored since clozapine can cause fatal agranulocytosis.[82] Also, quetiapine does not exacerbate motor symptoms of PD and may be considered for patients with PD and psychosis (Level C). Due to a better side effect profile, many clinicians may consider quetiapine as first-choice. Olanzapine and risperidone should not be used due to the potential for worsening motor function. Pimavanserin (Nuplazid) was not approved at the time of guideline development, but it is the only drug FDA-approved for the treatment of PD psychosis.[83]

In 2016, the APA published practice guidelines on the use of antipsychotics to treat agitation or psychosis in patients with dementia.[84] These guidelines do not specifically address the role of pimavanserin, but they do note that extrapyramidal side effects of other antipsychotic medications and the potential for cognitive worsening may be greater in individuals with Parkinson's disease dementia compared to other types of dementia.

An evidence-based review published in 2019 on behalf of the Movement Disorders Society found pimavanserin to be efficacious and to have an acceptable risk without requiring specialized monitoring.[85] Thus, the researchers concluded that its use for psychosis in PD is clinically useful, but they also state that there is a lack of safety data regarding durability beyond 6 weeks. Notably, they also weigh in on other agents in this class that are not indicated for PD psychosis, stating that olanzapine is not clinically useful (not efficacious), quetiapine is possibly useful (limited evidence), and

clozapine is also useful but requires specialized monitoring. They also emphasize that all antipsychotics should be used with great caution in demented patients with psychosis due to the risk of adverse effects (e.g., falls, impaired cognition, pneumonia, cardiovascular effects, stroke, and death).

PHARMACOLOGY[86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142]

First generation antipsychotics exert their therapeutic effect primarily by blockade of the dopamine-2 (D_2) receptors in the mesolimbic dopamine pathway. The blockade reduces the hyperactivity in this pathway and, thereby, potentially reduces the positive symptoms associated with psychosis. These agents also block the D_2 receptors in other pathways of the brain, resulting in their potential induction of negative and cognitive symptoms, extrapyramidal symptoms (EPS), tardive dyskinesia (TD), and hyperprolactinemia.

Antipsychotics block other receptors in varying degrees, largely resulting in additional adverse effects. Blockade of the muscarinic-cholinergic receptors can cause adrenergic blockade, which can result in orthostatic hypotension and drowsiness; dry mouth and blurred vision can be associated with the anticholinergic effects. Antagonism of the alpha-1 and histamine receptors has been proposed as one of the mechanisms leading to weight gain and drowsiness with antipsychotics.

The second generation antipsychotics (SGAs) are serotonin-dopamine antagonists. They differ from first generation antipsychotics (FGAs) in their "limbic-specific" dopamine type 2 (D_2)-receptor binding and high ratio of serotonin type 2 (5-HT_2) receptor binding to D_2 binding. These agents also have a lower affinity for D_2 receptors and, therefore, have faster dissociation with the receptor. Clinical properties that differentiate them from the FGAs are their reduced incidence of EPS and a decreased impact on prolactin levels.

Brexpiprazole (Rexulti) and cariprazine (Vraylar) are pharmacologically similar to aripiprazole (Abilify, Abilify Maintena, Abilify MyCite); all are partial dopamine agonists rather than pure dopamine antagonists and also have activity as 5-HT_{1A} agonists and 5-HT2A antagonists. Aripiprazole lauroxil (Aristada, Aristada Initio) is a prodrug of aripiprazole.

Pimavanserin (Nuplazid) is an inverse agonist/antagonist, primarily at the 5-HT_{2A} receptor, and to a lesser extent at the 5-HT_{2C} receptor. Pimavanserin was also shown to have no appreciable affinity for dopamine receptors and is therefore unlikely to impair motor function.

As indicated in the next table, effects of the SGAs on various receptors differ among agents. It is likely that the differences among these agents results from their varying effect on receptors other than their antagonism of 5-HT_{2A} and D_2 receptors. These ancillary pharmacologic properties include binding to D_1, D_3, and D_4 receptors; to 5-HT_{1A}, 5-HT_{2C}, 5-HT_3, 5-HT_6, and 5-HT_7 receptors; to α_1-adrenergic, α_2-adrenergic, histamine H_1, and muscarinic cholinergic receptors. While the clinical impact of activity at some of these receptors are not fully elucidated, others contribute to adverse effects (e.g. H_1 blockade and sedation).

Receptor Effects

Drug	Receptor Antagonist	Receptor Agonist	Receptors Bound with High Affinity	Receptors Bound with Moderate Affinity	Receptors Bound with Weak Affinity
First Generation Antipsychotics					
chlorpromazine	Adrenergic, peripheral anticholinergic, histaminergic, serotonergic	--	Adrenergic	--	Peripheral anticholinergic, histaminergic, serotonergic
fluphenazine	D_2, H_1, α, 5-HT_2	--	Not specified		
haloperidol	D_2, H_1, α, 5-HT_2	--	Not specified		
loxapine	D_2, α, M_1	--	Not specified		
loxapine inhalation powder (Adasuve)	D_2, H_1, α_2, 5-HT_2, M_1	--	$D_{1\text{-}4}$, 5-HT_2	--	--
molindone	D_2, α, 5-HT_2	--	--	--	D_2, α, 5-HT_2
perphenazine	D_2, H_1, α	--	Not specified		
pimozide (Orap)	D_2, others unspecified	--	Not specified		
thioridazine	D_2, H_1, α, 5-HT_2, M_1	--	Not specified		
thiothixene	D_2, H_1, α	--	D_2	--	H_1, α
trifluoperazine	D_2, H_1, α, 5-HT_2, M_1	--	Not specified		

D = dopamine
α = alpha
β = beta
5-HT = serotonin
M = muscarine
H = histamine
GABA = gamma aminobutyric acid
BZD = benzodiazepine
NE = norepinephrine

Receptor Effects (continued)

Drug	Receptor Antagonist	Receptor Agonist	Receptors Bound with High Affinity	Receptors Bound with Moderate Affinity	Receptors Bound with Weak Affinity
Second Generation Antipsychotics					
aripiprazole (Abilify, Abilify Maintena, Abilify MyCite, Aristada, Aristada Initio)	5-HT_{2A}, 5-HT_{2C}, 5-HT_7, α_1, H_1, 5-HT reuptake site	Partial agonist: D_2, 5-HT_{1A}	D_2, D_3, 5-HT_{1A}, 5-HT_{2A}	D_4, 5-HT_{2C}, 5-HT_7, α_1, H_1, 5-HT reuptake site	--
asenapine (Saphris)	D_2, 5-HT_{2A}	--	D_{1-4}, 5-HT_{1A-B}, 5-HT_{2A-C}, 5-HT_{5-7}, α_{1-2}, H_1	H_2	--
brexpiprazole (Rexulti)	5-HT_{2A}, 5-HT_{2B}, 5-HT_7, α_{1A}, α_{1B}, α_{1D}, α_{2C}	Partial agonist: D_2, D_3, 5-HT_{1A}	Not specified		
cariprazine (Vraylar)	5-HT_{2A}, 5-HT_{2B}, H_1	Partial agonist: D_2, D_3, 5-HT_{1A}	D_2, D_3, 5-HT_{2B}	5-HT_{2A}, H_1	--
clozapine (Clozaril, Fazaclo, Versacloz)	D_{1-5}, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, M_1, M_2, M_3, M_5, α_1, α_2, H_1	M_4	D_4	--	--
iloperidone (Fanapt)	D_2, 5-HT_2	--	D_{2-3}, 5-HT_{2A}	D_4, 5-HT_{6-7}, $NE\alpha_1$	D_1, 5-HT_{1A}, H_1
lurasidone (Latuda)	D_2, 5-HT_{2A}, 5-HT_7, α_{2A}	5-HT_{1A}	D_2, 5-HT_{2A}, 5-HT_7	α_{2C}	--
olanzapine (Zyprexa, Zyprexa Relprevv)	D_{1-4}, 5-HT_{2A}, 5-HT_{2C}, α_1, H_1, M_{1-5}	--	D_{1-4}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, α_1, H_1	5-HT_3, M_{1-5}	$GABA_A$, BZD, β
olanzapine/fluoxetine (Symbyax)	D_{1-4}, 5-HT_{2A}, 5-HT_{2C}, α_1, H_1, M_{1-5}	--	D_{1-4}, 5-HT_{2A}, 5-HT_{2C}, α_1, H_1, M_{1-5}	--	$GABA_A$, BZD, β
paliperidone ER (Invega, Invega Sustenna, Invega Trinza)	D_{1-4}, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, α_1, α_2, H_1	--	D_2, 5-HT_2, α_1, α_2, H_1	5-HT_{1C}, 5HT_{1D}, 5-HT_{1A}	D_1, haloperidol-sensitive sigma site
pimavanserin (Nuplazid)	5-HT_{2A}, 5-HT_{2C}	--	5-HT_{2A},	5-HT_{2C}	--
quetiapine (Seroquel)	D_1, D_2, 5-HT_{1A}, 5-HT_2, α_1, α_2, H_1	--	NE transporter with norquetiapine	--	--
quetiapine (Seroquel XR)	D_1, D_2, 5-HT_{1A}, 5-HT_{2A}, α_1b, α_2, H_1	--	NE transporter with norquetiapine	--	--
risperidone (Perseris, Risperdal, Risperdal Consta)	D_{1-2}, 5-HT_{1A}, 5-HT_{2A}, α_1, α_2, H_1	--	D_2, 5-HT_2, α_1, α_2, H_1	5-HT_{1C}, 5HT_{1D}, 5-HT_{1A}	D_1, haloperidol-sensitive sigma site
ziprasidone (Geodon)	D_2, 5-HT_{2A}, 5-HT_{2C}, 5-HT_{1B}, 5-HT_{1D}, α_1, H_1, synaptic 5-HT and NE reuptake	5-HT_{1A}	D_2, D_3, 5-HT_{2A}, 5-HT_{2C}, 5-HT_{1A}, 5-HT_{1D}, α_1	H_1	--

D = dopamine
5-HT = serotonin
GABA = gamma aminobutyric acid
α = alpha
M = muscarine
BZD = benzodiazepine
β = beta
H = histamine
NE = norepinephrine

PHARMACOKINETICS[143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188]

Drug	Bioavailability (%)	Half-life (hr)	Active Metabolites	CYP450 Enzyme System Substrate(s)
First Generation Antipsychotics – Oral				
amitriptyline	N/A	10–50	nortriptyline (half-life 20-100 hours)	3A4, 2C9, 2D6
chlorpromazine	19–51	23–37	7-hydroxychlorpromazine (half-life 10-40 hours)	2D6
fluphenazine	2.7 (oral)	18	--	2D6
haloperidol	60	24	hydroxyhaloperidol	3A4, 2D6
loxapine	N/A	4	multiple metabolites	1A2, 3A4, 2D6
molindone	N/A	12	--	--
perphenazine	N/A	9	--	2D6
pimozide (Orap)	40-50	55	--	3A4 (primary), 1A2, 2D6
thioridazine	N/A	24	mesoridazine and sulphoridazine	--
thiothixene	N/A	Biphasic 3.4 initial, 34 terminal	--	--
trifluoperazine	N/A	18	--	--
First Generation Antipsychotics – Injectable				
chlorpromazine hydrochloride	N/A	23–37	7-hydroxychlorpromazine (half-life 10-40 hours)	2D6
fluphenazine decanoate	N/A	--	--	2D6
fluphenazine hydrochloride	N/A	--	--	2D6
haloperidol decanoate (Haldol Decanoate)	N/A	3 weeks	hydroxyhaloperidol	3A4, 2D6
haloperidol lactate (Haldol)	N/A	--	hydroxyhaloperidol	3A4, 2D6
First Generation Antipsychotics – Inhaled				
loxapine inhalation powder (Adasuve)	N/A	7.61	multiple metabolites	1A2, 3A4, 2D6

IM = intramuscular; N/A = not available

Pharmacokinetics (continued)

Drug	Bioavailability (%)	Half-life (hr)	Active Metabolites	CYP450 Enzyme System Substrate(s)
Second Generation Antipsychotics – Oral				
aripiprazole (Abilify, Abilify MyCite)	87	75	dehydro-aripiprazole (half-life 94 hours)	2D6, 3A4
asenapine (Saphris)	35	24	--	1A2 (primary), 3A4, 2D6
brexpiprazole (Rexulti)	95	91	DM-3411 (half-life 86 hours; does not contribute to the therapeutic effects of brexpiprazole)	2D6, 3A4
cariprazine (Vraylar)	N/A	48–96	desmethyl cariprazine (DCAR), didesmethyl cariprazine (DDCAR)	3A4 (primary), 2D6
clozapine (Clozaril, Fazaclo, Versacloz)	N/A	12	--	1A2, 2D6, 3A4
iloperidone (Fanapt)	well absorbed	18-33	P88 (half-life 26-37 hours)	2D6, 3A4
lurasidone (Latuda)	9–19	18	ID-14283, ID-14326	3A4
olanzapine (Zyprexa)	>57	21-54	--	1A2, 2D6
olanzapine/ fluoxetine (Symbyax)	N/A	21–54 / 4–6 days	norfluoxetine (half-life 16 days)	1A2, 2D6
paliperidone ER (Invega)	28	23	--	2D6 (primary), 3A4
pimavanserin (Nuplazid)	N/A	57	AC-279	3A4 (primary), 3A5, 2J2, 2D6
quetiapine (Seroquel)	100	6	N-desalkyl quetiapine (norquetiapine)	3A4
quetiapine ER (Seroquel XR)	N/A	7	N-desalkyl quetiapine (norquetiapine)	3A4
risperidone (Risperdal)	70	3 (extensive metabolizers); 20 (poor metabolizers)	9-hydroxyrisperidone (paliperidone) (half-life of 21 hours in extensive metabolizers and 30 hours in poor metabolizers)	2D6
ziprasidone (Geodon)	60	7	--	3A4 (primary), 1A2

Pharmacokinetics (continued)

Drug	Bioavailability (%)	Half-life (hr)	Active Metabolites	CYP450 Enzyme System Substrate(s)
Second Generation Antipsychotics – Injectable				
aripiprazole ER (Abilify Maintena)	N/A	29.9–46.5 days	dehydro-aripiprazole	2D6, 3A4
aripiprazole lauroxil ER (Aristada, Aristada Initio)	N/A	53.9–57.2 days (Aristada) 15 to 18 days (Aristada Initio)	dehydro-aripiprazole	2D6, 3A4
olanzapine (Zyprexa)	N/A	21–54	--	1A2, 2D6
olanzapine (Zyprexa Relprevv)	N/A	30 days	--	1A2, 2D6
paliperidone palmitate (Invega Sustenna)	N/A	25–49 days	paliperidone	2D6 (primary), 3A4
paliperidone palmitate (Invega Trinza)	N/A	84–95 days (deltoid injections); 118-139 days (gluteal injections)	paliperidone	2D6 (primary), 3A4
risperidone ER microspheres (Risperdal Consta)	N/A	72–144	9-hydroxyrisperidone (paliperidone)	2D6
risperidone ER suspension (Perseris)	N/A	216–264	9-hydroxyrisperidone (paliperidone)	2D6
ziprasidone (Geodon)	100	2–5	--	3A4 (primary), 1A2

IM = intramuscular; N/A = not available

CONTRAINDICATIONS/WARNINGS[189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232]

Contraindications

Do not use an agent in patients with known hypersensitivity to that particular agent. Cross-sensitivity may also occur in agents with similar structural components of the parent drug or metabolite (e.g., hypersensitivity to other phenothiazines or between risperidone and paliperidone). Severe hypersensitivity reactions, including life threatening reactions such as Stevens-Johnson syndrome or angioedema have been reported with select agents.

Concomitant use of clozapine (Clozaril, Fazaclo, Versacloz) with other agents that have the potential to cause severe neutropenia, or otherwise suppress bone marrow function, is contraindicated. Clozapine is contraindicated in patients with myeloproliferative disorders, uncontrolled epilepsy, paralytic ileus, history of clozapine-induced blood dyscrasias, and severe central nervous system (CNS) depression or comatose states.

Similarly, chlorpromazine, fluphenazine, haloperidol, loxapine, molindone, perphenazine, pimozide (Orap), thioridazine, and trifluoperazine are contraindicated in patients who are comatose or have greatly depressed states because of CNS depressants or other causes.

Fluphenazine, perphenazine, and trifluoperazine are contraindicated in patients with blood dyscrasias, bone marrow depression, or pre-existing liver damage. Fluphenazine is contraindicated in the presence of suspected or established subcortical brain damage.

Haloperidol is contraindicated in patients with Parkinson's disease and dementia with Lewy bodies.

Thiothixene is contraindicated in the presence of circulatory collapse or blood dyscrasias.

Pimozide is contraindicated in the treatment of simple tics or tics other than those associated with Tourette's disorder. Pimozide should not be taken by patients who are taking other drugs that may cause motor or phonic tics.

The QT interval is prolonged by pimozide, so patients with cardiac conduction abnormalities should not take this drug. For similar reasons, use of pimozide concurrently with CYP3A4 inhibitors (such as macrolide antibiotics, azole antifungals, or protease inhibitors) is contraindicated.

Thioridazine is contraindicated for co-administration with other drugs that prolong the QT interval and in patients with congenital long QT syndrome or history of cardiac arrhythmias. Thioridazine is also contraindicated in patients with hypertensive or hypotensive heart disease of extreme degree.

Loxapine inhalation powder (Adasuve) is contraindicated in patients with a current diagnosis or history of asthma, COPD, or other lung disease associated with bronchospasm or current use of medications to treat airways disease (asthma or COPD). Inhaled loxapine should not be taken by patients with acute respiratory symptoms or signs, such as wheezing, or by patients with a history of bronchospasm following inhaled loxapine treatment.

Co-administration with strong CYP3A4 inhibitors or inducers is contraindicated with lurasidone (Latuda).

Boxed Warnings

All antipsychotics, including pimavanserin (Nuplazid), have a boxed warning regarding an increased incidence of mortality when these agents are used in elderly patients with dementia-related psychosis.[233] A review of 17 placebo-controlled trials revealed a rate of death in the elderly patients who received second generation antipsychotics of approximately 4.5% as compared to a rate of approximately 2.6% in placebo-treated patients. The causes of death were varied.

Aripiprazole (Abilify, Abilify Mycite), lurasidone (Latuda), olanzapine/fluoxetine (Symbyax), and quetiapine (Seroquel, Seroquel XR) have the same boxed warning as the antidepressants in regards to an increased risk of suicidality in children, adolescents, and young adults; therefore, close monitoring for signs and symptoms of suicidality in this patient population should occur.

Clozapine (Clozaril, Fazaclo, Versacloz) has several additional boxed warnings:

- Due to a significant risk of severe neutropenia (absolute neutrophil count < 500/µL), which may increase the risk of serious and potentially fatal infections, clozapine is only available through the Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program. Risk of severe neutropenia is greatest during the first 18 weeks of treatment, but the cause is unknown and it is not dose-

dependent. See prescribing information for clozapine products and the Clozapine REMS Program (www.clozapinerems.com) for absolute neutrophil count (ANC) monitoring details. Patients must have a baseline white blood cell (WBC) count and ANC assessed before initiation of treatment and regularly during treatment.

- Seizures are associated with the use of clozapine (cumulative incidence at 1 year of 5%); this is a dose-related effect. Caution must be used when administering clozapine to patients with a history of seizures or predisposition to seizures. Patients must also be warned to avoid engaging in activities where a loss of consciousness may cause harm to themselves or others.
- Myocarditis occurs with clozapine at a rate of 5 cases per 100,000 patient years; over half of these cases were fatal. Clozapine also carries warnings for cardiomyopathy and mitral valve incompetence.

Orthostatic hypotension with rare collapse (1 case per 3,000 patients) and respiratory and/or cardiac arrest occur at a higher rate in patients receiving clozapine, especially during dose escalation in the initial titration phase. The incidence also appears higher in patients receiving other psychotropic drugs.

Loxapine inhalation powder (Adasuve) has a boxed warning cautioning of bronchospasms that can potentially lead to respiratory distress and respiratory arrest. Healthcare facilities administering loxapine inhalation powder must have access to short-acting bronchodilators for immediate treatment of bronchospasms.

Olanzapine (Zyprexa Relprevv) has a boxed warning stating that patients are at risk for Post-injection Delirium Sedation Syndrome (PDSS). This syndrome may result in severe sedation, including coma, and/or delirium after each injection. Patients should be observed for at least 3 hours in a healthcare facility with access to emergency response services following administration.

Thioridazine has a boxed warning regarding its tendency to prolong the QTc interval in a dose-related manner.

FGA Warnings

Drug	Elderly Patients with Dementia Psychosis	Suicide	Hyperglycemia	Dyslipidemia	Hyperprolactinemia	Weight Gain	Tardive Dyskinesia	Priapism	Use in Patients with Concomitant Illness	Orthostatic Hypotension	Leukopenia, Neutropenia, Agranulocytosis	QT Prolongation	Seizures	Neuroleptic Malignant Syndrome	Potential for Cognitive and Motor Impairment	Dysphagia	Body Temperature Regulation Disruption	Increases in Blood Pressure in Children and Adolescents	Suicidality in Children and Adolescents
amitriptyline/ perphenazine	X	X	-	-	X	-	X	-	X	X	X	-	X	X	X	-	X	-	X
chlorpromazine products	X	-	-	-	X	-	X	-	X	X	X	-	X	X	X	-	X	-	-
fluphenazine products	X	-	-	-	X	-	X	-	X	-	X	-	X	X	X	-	X	-	-
haloperidol products	X	-	-	-	X	-	X	-	X	-	X	X	X	X	X	-	X	-	-
loxapine	X	-	-	-	-	-	X	-	X	X	-	-	X	X	X	-	-	-	-
loxapine inhalation powder (Adasuve)	X	-	-	-	-	-	-	-	-	X	-	-	X	X	X	-	-	-	-
molindone	X	-	-	-	X	-	X	-	X	-	X	-	X	X	X	-	-	-	-
perphenazine	X	-	-	-	X	-	X	-	X	X	X	-	X	X	X	-	X	-	-
pimozide (Orap)	X	-	-	-	X	-	X	-	X	-	X	X	X	X	X	-	X	-	-
thioridazine	X	-	-	-	X	-	X	-	X	-	X	X	X	X	X	-	-	-	-
thiothixene	X	-	-	-	X	-	X	-	X	-	X	-	-	X	X	-	-	-	-
trifluoperazine	X	-	-	-	X	-	X	-	X	-	X	-	X	X	X	-	-	-	-

SGA Warnings

Drug	Elderly Patients with Dementia Psychosis	Suicide	Hyperglycemia	Dyslipidemia	Hyperprolactinemia	Weight Gain	Tardive Dyskinesia	Priapism	Use in Patients with Concomitant Illness	Orthostatic Hypotension	Leukopenia, Neutropenia, Agranulocytosis	QT Prolongation	Seizures	Neuroleptic Malignant Syndrome	Potential for Cognitive and Motor Impairment	Dysphagia	Body Temperature Regulation Disruption	Increases in Blood Pressure in Children and Adolescents	Suicidality in Children and Adolescents
aripiprazole (Abilify, Abilify Mycite)	X	X	X	X	-	X	X	-	X	X	X	-	X	X	X	X	X	-	X
aripiprazole ER (Abilify Maintena)	X	-	X	X	-	X	X	-	X	X	X	-	X	X	X	X	X	-	-
aripiprazole lauroxil ER (Aristada, Aristada Initio)	X	-	X	X	-	X	X	-	-	X	X	-	X	X	X	X	X	-	-
asenapine (Saphris)	X	X	X	X	X	X	X	-	X	X	X	X	X	X	X	X	X	-	-
brexpiprazole (Rexulti)	X	X	X	X	-	X	X	-	-	X	X	-	X	X	X	X	X	-	X
cariprazine (Vraylar)	X	X	X	X	-	X	X	-	-	X	X	-	X	X	X	X	X	-	-
clozapine (Clozaril, Fazaclo, Versacloz)*	X	-	X	X	-		X	X	X	X	X	X	X	X	X	X	-	-	-
iloperidone (Fanapt)	X	X	X	X	X	X	X	X	-	X	X	X	X	X	X	X	X	-	-
lurasidone (Latuda)	X	X	X	X	X	X	X	-	X	X	X	-	X	X	X	X	X	-	-
olanzapine oral (Zyprexa)	X	X	X	X	X	X	X	X	X	X	X	-	X	X	X	X	X	-	-
paliperidone ER (Invega)	X	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
paliperidone palmitate (Invega Sustenna, Invega Trinza)	X	-	X	X	X	X	X	X	-	X	X	X	X	X	X	X	X	-	-

SGA Warnings (continued)

Drug	Elderly Patients with Dementia Psychosis	Suicide	Hyperglycemia	Dyslipidemia	Hyperprolactinemia	Weight Gain	Tardive Dyskinesia	Priapism	Use in Patients with Concomitant Illness	Orthostatic Hypotension	Leukopenia, Neutropenia, Agranulocytosis	QT Prolongation	Seizures	Neuroleptic Malignant Syndrome	Potential for Cognitive and Motor Impairment	Dysphagia	Body Temperature Regulation Disruption	Increases in Blood Pressure in Children and Adolescents	Suicidality in Children and Adolescents
pimavanserin (Nuplazid)	X	-	-	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-
quetiapine (Seroquel)†	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
quetiapine ER (Seroquel XR)†	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
risperidone oral (Risperdal)	X	-	X	X	X	X	X	X	-	X	X	-	X	X	X	X	X	-	-
risperidone ER injectable (Perseris, Risperdal Consta)	X	X‡	X	X	X	X	X	X	X	X	X	-	X	X	X	X	X	-	-
ziprasidone oral (Geodon) §	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
olanzapine/ fluoxetine (Symbyax)	X	X	X	X	X	X	X	X	X	X	X	-	X	X	X	X	X	-	-

* Due to the risk of agranulocytosis, all clozapine products are available only through a restricted program to which prescribers, patients, and pharmacies must enroll.

† Lens changes have been observed in patients using quetiapine long term.

‡ Perseris only

§ Ziprasidone should be discontinued in patients who develop a rash if there is no other identifiable cause.

Other Warnings

All first generation antipsychotics (FGAs) and second generation antipsychotics (SGAs) have warnings regarding neuroleptic malignant syndrome (NMS), characterized by rigidity, hyperthermia, and autonomic instability (hypertension and tachycardia). NMS is a rare event usually occurring within the first week after treatment initiation or dose increase. Risk factors include acute agitation, young age, male gender, preexisting neurological disability, physical illness, dehydration, rapid escalation of antipsychotic dose, use of high-potency or intramuscular agent.[234]

Antipsychotics may reduce the body's ability to regulate core body temperature; caution should be used in patients who will be experiencing conditions contributing to an increased core body temperature (e.g., strenuous exercise, extreme heat exposure).

In addition, significant neurotoxicity, including rigidity and inability to speak, may occur in patients using an antipsychotic who also have thyrotoxicosis.

All antipsychotics, except loxapine inhalation powder (Adasuve), share a warning that tardive dyskinesia (TD) may develop in patients treated with these drugs. Likewise, antipsychotic treatment may suppress the signs and symptoms of the syndrome, possibly masking the underlying process. The risk of TD is higher among the elderly and highest among elderly women. The risk of developing TD and the likelihood that it will become irreversible are thought to increase with treatment duration; discontinuation of therapy should be considered; however, the syndrome may remit once an antipsychotic is withdrawn (partially or completely). Nonetheless, treatment may be required despite symptoms.

Patients with Parkinson's disease or Lewy body dementia may experience increased sensitivity to some of these agents, which can manifest in confusion, obtundation, postural instability, extrapyramidal symptoms, and NMS. Extrapyramidal symptoms, such as parkinsonism, dystonias, and akathisia, are associated especially with use of the FGAs and to varying degrees with some of the SGAs, particularly higher doses of risperidone.

Cerebrovascular adverse reactions, including stroke, have been reported in elderly patients with dementia treated with SGAs; these agents are not approved for dementia-related psychosis. Antipsychotics should be administered cautiously in patients with severe cardiovascular disorders, severe respiratory disorders, and seizure disorders, as well as in patients on other agents with a significant CNS depressant effect. Antipsychotics have the potential to cause cognitive and motor impairment. Likewise, esophageal dysmotility and aspiration have been associated with antipsychotics.

Leukopenia, neutropenia, and agranulocytosis have been reported with FGAs and SGAs. Patients with a history of a clinically significant low WBC or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy. Consider discontinuation of antipsychotic therapy if decreases of CBC from baseline occur.

An encephalopathic syndrome followed by irreversible brain damage has been reported when haloperidol and lithium have been used in combination; patients should be monitored closely for neurological toxicity when both are used together.

Agents with significant anticholinergic effects should be used cautiously in patients with glaucoma/increased intraocular pressure, constipation, significant prostatic hypertrophy, or those with a tendency for urinary retention.

Ocular toxicity may occur with loxapine. Ocular adverse effects in animals have also been reported with several other antipsychotics, including phenothiazines and quetiapine.

Cases of bronchopneumonia have been reported in patients taking antipsychotics, possibly due to lethargy and decreased sensation of thirst as a result of CNS inhibition, which may lead to dehydration, hemoconcentration, and a reduction in pulmonary ventilation. Corrective therapy should be administered promptly.

Postural hypotension may occur with all antipsychotics, particularly immediate-acting injectables and during dose increases. Falls also may result from somnolence and motor and sensory instability, which may also occur with antipsychotics. Patients should have initial and recurring fall assessments due to these potential adverse effects, and prescribers should consider other medications or conditions that may exacerbate these effects or increase the risk of a fall.

SGAs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain. Monitor patients for symptoms of hyperglycemia, including polydipsia, polyuria, polyphagia, and weakness. Cases of extreme hyperglycemia associated with diabetic ketoacidosis (DKA), hyperosmolar coma, or death have reported. Monitor glucose regularly in patients with diabetes or at risk for diabetes. Undesirable alterations in lipid levels have been observed in patients treated with atypical antipsychotics. Significant weight gain has been reported and should be monitored.

Prolactin elevation may also occur with agents that act as dopamine antagonists, while the risk is notable with higher-potency FGAs (e.g., haloperidol, fluphenazine), hyperprolactinemia may also occur with SGAs, particularly risperidone (Perseris, Risperdal, Risperdal Consta) and paliperidone (Invega, Invega Sustenna, Invega Trinza).

Among the SGAs, asenapine (Saphris), clozapine (Clozaril, Fazaclo, Versacloz), iloperidone (Fanapt), olanzapine/fluoxetine (Symbyax), paliperidone ER (Invega), paliperidone palmitate (Invega Sustenna, Invega Trinza), pimavanserin (Nuplazid), quetiapine (Seroquel, Seroquel XR), and ziprasidone (Geodon) have a warning of QT prolongation and risk of sudden death. This risk is also notable with FGAs. The warning states to avoid the use of these drugs in combination with other drugs that are known to prolong the QT interval, in patients with congenital long QT syndrome, and in patients with a history of cardiac arrhythmias. Asenapine had a prolonged QT interval of 2 to 5 msec compared to placebo. Paliperidone causes a modest increase in the QT interval (~12 msec). Iloperidone prolongs the QT interval by 9 msec, on average. Paliperidone causes a modest increase in the QT interval (~12 msec). Ziprasidone had an average increase of 20 msec in the QT interval, about 9 to 14 msec longer than risperidone (Risperdal), olanzapine (Zyprexa), quetiapine, and haloperidol, but 14 msec shorter than thioridazine, which has been shown to prolong the QT interval. These products should be avoided in circumstances that may increase the risk of torsades de pointes and/or sudden death including a history of cardiac arrhythmias, such as bradycardia, hypokalemia, hypomagnesemia, and presence of congenital prolongation of the QT interval. The use of quetiapine and clozapine should also be avoided in combination with other drugs that prolong QT interval including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class III antiarrhythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), citalopram (dose dependent), or any other class of medications known to prolong the QTc interval (e.g., pentamidine, levomethadyl acetate, methadone). Caution should be exercised when quetiapine and clozapine is prescribed in patients with increased risk of QT prolongation (e.g.,

cardiovascular disease, family history of QT prolongation, the elderly, congestive heart failure, and heart hypertrophy).

A retrospective cohort study of Medicaid enrollees in Tennessee demonstrated that there is an increased risk of sudden cardiac death for users of first and second generation antipsychotics.[235] The study compared users of typical antipsychotics (n=44,218), second generation antipsychotics (n=46,089), and non-users of antipsychotic drugs (n=186,600). Primary analysis demonstrated that users of typical and second generation antipsychotics had higher rates of sudden cardiac death than non-users, which was demonstrated by the adjusted incidence-rate ratios of 1.99 (95% confidence interval [CI], 1.68 to 2.34) and 2.26 (95% CI, 1.88 to 2.72), respectively. The risk increased correspondingly with increased doses of second generation antipsychotics with the incidence-rate ratio of low doses at 1.59 (95% CI, 1.03 to 2.46) and increasing to 2.86 (95% CI, 2.25 to 3.65) for high doses (p=0.01). In contrast, the incidence-rate ratio 1.13 (95% CI, 0.98 to 1.3) of former users of antipsychotic drugs did not reveal an increased risk for sudden cardiac death; this risk returns to baseline after the patient discontinues use of the antipsychotics.

In 2016, the FDA issued a drug safety communication regarding impulse-control problems associated with aripiprazole-containing products (Abilify, Abilify Mycite, Abilify Maintena, Aristada), including compulsive or uncontrollable urges related to gambling, shopping/spending money, binge eating, and sexual behavior.[236] These behaviors were reported primarily in patients without a history of impulse-control problems, most of which were related to gambling. In most cases, these urges ceased once aripiprazole was discontinued or following a dose reduction. Gambling has been reported in post-marketing studies as an adverse effect; however, as a result of the FDA communication, a warning regarding impulse-control problems has been added to all labels of aripiprazole-containing products. Healthcare professionals should advise patients and caregivers of this risk and instruct them to discuss this with a healthcare professional if they suspect they are experiencing this behavior; patients should not discontinue aripiprazole abruptly. In 2018, the labeling for brexpiprazole (Rexulti) was updated to include a warning regarding pathological gambling and other compulsive behaviors as well based on postmarketing case reports with brexpiprazole. Discontinuation or a dose reduction may be required if a patient develops such urges.

Cariprazine (Vraylar) also carries a warning for late-occurring adverse reactions. This is likely due to its (and its metabolites') long half-life and the potential for accumulation.

Abrupt discontinuation of haloperidol (Haldol) may result in transient dyskinetic signs that may be indistinguishable from tardive dyskinesia except for duration. Gradual withdrawal of haloperidol is recommended.

Clozapine (Clozaril, Fazaclo, Versacloz) has a warning regarding a 1% incidence of eosinophilia occurring in patients. Hepatotoxicity, including hepatic failure, hepatic necrosis, and hepatitis, has been reported in patients treated with clozapine.

Cases of impaired liver function and/or jaundice have been reported with haloperidol and haloperidol decanoate (Haldol Decanoate); however, neither product carries a warning for hepatic impairment.

Olanzapine/fluoxetine (Symbyax) has warnings regarding serotonin syndrome, allergic reaction and rash, activation of mania/hypomania, abnormal bleeding, and hyponatremia. As a result of pupillary dilation that occurs following the use of many antidepressants, including olanzapine/fluoxetine

(Symbyax), an angle-closure attack may occur in a patient with anatomically narrow angles who does not have a patent iridectomy.

Warnings for olanzapine long-acting injection include risk of suicide, hyperlipidemia, and weight gain.

In 2016, the FDA issued a drug safety communication regarding the risk of drug reaction with eosinophilia and systemic symptoms (DRESS) with all products containing olanzapine (Zyprexa, Symbyax).[237] DRESS, a life-threatening reaction, often begins as a rash and generally causes hematologic abnormalities. Patients should be advised to seek medical treatment immediately if they develop a fever with a rash and swollen lymph glands or swelling of the face. If DRESS is suspected, immediate discontinuation of olanzapine is recommended. Labeling for agents containing olanzapine have been updated to reflect this warning. Ziprasidone and quetiapine also carry a warning regarding DRESS and should also be discontinued if DRESS is suspected.

Oral paliperidone (Invega) has a warning against its use in patients with pre-existing severe gastrointestinal narrowing. Reports of obstructive symptoms in patients with strictures are associated with ingestion of drugs that have non-deformable controlled-release formulations. Because of the design, the drug should only be used in patients who can swallow the tablet whole. Notably, this tablet is passed in the feces; patients may notice a "ghost pill" and should be advised of the medication's release system. Other warnings for oral paliperidone include thrombotic thrombocytopenic purpura (TTP) and antiemetic effect. Intramuscular risperidone also has similar warnings. This formulation also carries a warning for osteodystrophy and tumors in animals. Orally disintegrating risperidone (Risperdal) tablets contain phenylalanine; they should be avoided in patients with phenylketonuria.

In May 2018, Acadia Pharmaceuticals issued a press release regarding the safety risk of pimavanserin (Nuplazid) due to reports of serious adverse events through the FDA Adverse Events Reporting System (FAERS) database.[238,239] As of May 2018, over 1,800 serious cases (including over 700 deaths) were reported through the FAERS database. The FDA noted that the reported cases most often involved geriatric patients with advanced Parkinson's disease and many medical conditions (with several concomitant medications with risks for serious adverse events). Both Acadia and the FDA reiterated that they were continuing to monitor the reported events. In September 2018, the FDA reported they had completed their review of the cases and did not identify any new or unexpected safety findings or findings inconsistent with the product labeling.[240] However, they did notice some concerns in prescribing patterns, particularly related to the concomitant use of other antipsychotics or other agents that can cause QT prolongation. As a result, in their update, they reminded prescribers that only pimavanserin is approved for the treatment of Parkinson's disease psychosis.

Quetiapine ER has warnings for withdrawal symptoms upon discontinuation, and risks for cataracts, hypothyroidism, and transaminase elevations. Quetiapine also has a warning for cataract risk.

Risk Evaluation and Mitigation Strategy (REMS)[241]

Injectable olanzapine (Zyprexa Relprevv) requires the prescriber, pharmacy, and patient to be enrolled in the Zyprexa Relprevv Patient Care Program. Also required are assurances of the implementation of elements to ensure safe use, such as special certification of healthcare providers and dispensing pharmacies, patient registration, and continued monitoring of patients using the injection. Due to the life-threatening risk of agranulocytosis, all clozapine products share a REMS program: the Clozapine REMS Program. The program requires prescribers to be certified to prescribe clozapine, and patients and pharmacies must be enrolled in the clozapine REMS program to ensure safe use. The program

provides educational material on agranulocytosis and required neutrophil laboratory monitoring details. Prior to this shared REMS program, prescribers, pharmacies, and patients were required to enroll in each manufacturer's individual monitoring website, which made monitoring continuity difficult when patients changed clozapine formulations.[242] Loxapine inhalation powder (Adasuve) is available only through a restricted program called the Adasuve REMS. Loxapine inhalation powder should only be administered in an enrolled healthcare facility that has immediate access on-site to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation or mechanical ventilation). Wholesalers and distributors must enroll in the program and distribute only to enrolled healthcare facilities.

DRUG INTERACTIONS[243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289]

Drug	SSRIs	Phenytoin (P)	CYP3A4 Inducers	CYP3A4 Inhibitors	CYP2D6 Inhibitors
First Generation Antipsychotics					
amitriptyline/ perphenazine	May ↑ concentration of amitriptyline	Causes P levels to fluctuate, amitriptyline may lower seizure threshold	May ↓ concentration of amitriptyline	May ↑ concentration of amitriptyline	May ↑ concentration of amitriptyline
chlorpromazine	--	Causes P levels to fluctuate	--	--	May ↑ concentration of chlorpromazine
fluphenazine	--	Causes P levels to fluctuate	--	--	May ↑ concentration of fluphenazine
haloperidol	Fluoxetine ↑ concentration of haloperidol	--	Therapeutic effect of haloperidol decreased; may increase carbamazepine levels	May ↑ concentration of haloperidol	May ↑ concentration of haloperidol
loxapine	--	--	--	--	--
loxapine inhalation powder (Adasuve)	--	--	--	--	--
molindone	--	--	--	--	--
perphenazine	--	Causes P levels to fluctuate	--	--	May ↑ concentration of perphenazine

Drug interactions in the above table are selective, and are not meant to be all inclusive.

Drug Interactions (continued)

Drug	SSRIs	Phenytoin (P)	CYP3A4 Inducer	CYP3A4 Inhibitors	CYP2D6 Inhibitors
First Generation Antipsychotics *(continued)*					
pimozide (Orap)	Citalopram may additively ↑ QTc values Other SSRIs may↑ concentration of pimozide Contraindicated	--	--	May ↑ concentration of pimozide	May ↑ concentration of pimozide
thioridazine	May ↑ concentration of thioridazine Contraindicated	Causes P levels to fluctuate	--	--	--
thiothixene	--	--	--	--	--
trifluoperazine	Fluoxetine and citalopram may prolong QTc	Causes P levels to fluctuate	--	--	--
Second Generation Antipsychotics					
aripiprazole (Abilify, Abilify Mycite) A = aripiprazole	--	--	↓ Cmax and AUC of A; double dose of A	Ketoconazole and itraconazole increase AUC of A; ↓ A dose by half	Quinidine, fluoxetine, paroxetine increase AUC of A; ↓ A dose by half
aripiprazole ER (Abilify Maintena) AER = aripiprazole	--	--	↓ concentration of AER; avoid use for > 14 days	↑ concentration of AER; reduction of AER dose is recommended	↑ concentration of AER; reduction of AER dose is recommended
aripiprazole lauroxil ER (Aristada) ALER = aripiprazole	--	--	↓ concentration of ALER; avoid use for > 14 days	↑ concentration of ALER; reduction of ALER dose is recommended	↑ concentration of ALER; reduction of ALER dose is recommended
aripiprazole lauroxil ER (Aristada Initio) ALER = aripiprazole	--	--	↓ concentration of ALER; avoid concurrent use	↑ concentration of ALER; avoid concurrent use	↑ concentration of ALER; avoid concurrent use
asenapine (Saphris) A = asenapine	--	--	--	--	May ↓ clearance of A; A may ↓ clearance of substrates

Drug interactions in the above table are selective, and are not meant to be all inclusive.

Drug Interactions (continued)

Drug	SSRIs	Phenytoin (P)	CYP3A4 Inducer	CYP3A4 Inhibitors	CYP2D6 Inhibitors
Second Generation Antipsychotics *(continued)*					
brexpiprazole (Rexulti) B = brexpiprazole	--	--	Exposure of B decreased; double the usual dose of B and further adjust based on clinical response	↑ exposure of B; administer half of the usual B dose	↑ exposure of B; administer half of the usual B dose
cariprazine (Vraylar) C = cariprazine	--	--	Exposure of C decreased; concomitant use not recommended	↑ exposure of C; administer half of the usual C dose	--
clozapine (Clozaril, Fazaclo, Versacloz) CL = clozapine	Fluvoxamine ↑ trough concentration of CL and its metabolites; consider lower dose of CL	P may ↓ CL plasma levels	Concomitant use is advised against. Other inducers not recommended, Carbamazepine may increase risk of agranulocytosis	Cimetidine and erythromycin may ↑ plasma levels of CL	Use with caution with these agents
iloperidone (Fanapt) I = iloperidone	--	--	--	May ↑ concentration of I	May ↑ concentration of I
lurasidone (Latuda)	--	--	Strong inducers contraindicated May be necessary to increase dose with moderate inducers	Strong inhibitors contraindicated Reduce dose by one-half with moderate inhibitors	--
olanzapine (Zyprexa)* O = olanzapine	Fluvoxamine ↑ O AUC; consider lower doses of O	--	CBZ ↑ clearance of O	--	--
paliperidone ER (Invega) P = paliperidone	Citalopram can increase QTc prolongation, paroxetine may increase plasma levels of P	--	CBZ ↑ renal clearance of P; it may be necessary to ↑ P dose when co-administered with a strong inducer of both CYP3A4 and P-glycoprotein (P-gp)	--	--

Drug interactions in the above table are selective, and are not meant to be all inclusive.

* The drug-drug interactions of the individual components, fluoxetine (Prozac®) and olanzapine (Zyprexa), are applicable to Symbyax.

Drug Interactions (continued)

Drug	SSRIs	Phenytoin (P)	CYP3A4 Inducer	CYP3A4 Inhibitors	CYP2D6 Inhibitors
Second Generation Antipsychotics *(continued)*					
paliperidone palmitate (Invega Sustenna)† PP = paliperidone palmitate	--	--	Avoid co-administration of strong inducers of both CYP3A4 and P-gp; if use cannot be avoided, consider using the oral tablets	Avoid coadministering with a strong inhibitor; consider use of oral paliperidone if a strong inducer is required	--
paliperidone palmitate (Invega Trinza)† PP = paliperidone palmitate	--	--	Avoid co-administration of strong inducers of both CYP3A4 and P-gp; if use cannot be avoided, consider using the oral tablets	--	--
pimavanserin (Nuplazid) PI = pimavanserin	--	--	Concurrent use may decrease efficacy; dose adjustment may be needed	Concurrent use may increase exposure; dose adjustment may be needed (reduce PI dose in half with strong inhibitors)	--
quetiapine (Seroquel, Seroquel XR) Q = quetiapine	Citalopram and fluoxetine can increase QTc prolongation	P ↑ clearance of Q by 5-fold; increased doses of Q may be needed	Monitor, increased doses of Q may be needed	Ketoconazole ↓ clearance of Q; use caution with Q and all these agents	--
risperidone (Perseris, Risperdal, Risperdal Consta) R = risperidone	Fluoxetine can increase the plasma level of R	P likely to ↑ clearance of R and active metabolite	CBZ ↑ clearance of R and active metabolite	Itraconazole ↑ levels of R	Paroxetine ↑ levels of R
ziprasidone (Geodon) Z = ziprasidone	Citalopram can increase QTc prolongation	--	CBZ ↓ Z AUC	Ketoconazole ↑ Z AUC	--

Drug interactions in the above table are selective, and are not meant to be all inclusive.

† Because paliperidone palmitate is hydrolyzed to paliperidone, results from studies with oral paliperidone should be taken into consideration when assessing drug-drug interaction potential.

ADVERSE EFFECTS[290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333]

Drug	EPS	Glucose Abnormalities	Dyslipidemia	Hypotension	Prolactin Elevation	Sedation	Weight Gain	Anticholinergic Effects	QT Prolongation
First Generation Antipsychotics – Oral									
amitriptyline/ perphenazine	reported	reported	nr	reported	reported	reported	reported	reported	reported
chlorpromazine	reported	reported	nr	reported	reported	reported	reported	reported	reported
fluphenazine	reported	nr	nr	reported	reported	reported	nr	reported	nr
haloperidol	reported	reported	nr	reported	reported	reported	nr	reported	reported
loxapine	reported	nr	nr	reported	reported	reported	reported	reported	nr
molindone	reported	nr	nr	reported	reported	reported	reported	reported	nr
perphenazine	reported	reported	nr	reported	reported	reported	reported	reported	nr
pimozide (Orap)	reported	nr	nr	nr	0	70	reported	reported	reported
thioridazine	reported	nr	nr	reported	reported	reported	reported	reported	reported
thiothixene	reported	reported	nr	reported	reported	reported	reported	reported	nr
trifluoperazine	reported	reported	nr	reported	reported	reported	reported	reported	nr
First Generation Antipsychotics – Injectable*									
chlorpromazine hydrochloride	reported	reported	nr	reported	reported	reported	reported	reported	reported
fluphenazine decanoate	reported	nr	nr	reported	reported	reported	nr	reported	nr
fluphenazine hydrochloride	reported	reported	nr	reported	reported	reported	reported	reported	nr
haloperidol decanoate (Haldol Decanoate)	reported	reported	nr	reported	reported	reported	reported	reported	reported
haloperidol lactate (Haldol)	reported	reported	nr	reported	reported	reported	reported	reported	reported

Adverse effects are reported as a percentage. Adverse effects are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

* Injection site reactions have been reported with injectable agents.

Adverse Effects (continued)

Drug	EPS	Glucose Abnormalities	Dyslipidemia	Hypotension	Prolactin Elevation	Sedation	Weight Gain	Anticholinergic Effects	QT Prolongation
First Generation Antipsychotics – Inhaled									
loxapine inhalation powder (Adasuve)	nr	nr	nr	0.4	nr	nr	nr	reported	nr
Second Generation Antipsychotics – Oral									
aripiprazole (Abilify, Abilify Mycite†)	2–20 (0–3)	reported	reported	reported	reported	4–21 (2-4)	2–3 (1-2)	2–11 (0–7)	nr
asenapine (Saphris)‡	4–12 (2-7)	reported	reported	nr	reported	13–24 (6-7)	2–5 (< 1)	nr	reported
brexpiprazole (Rexulti)	2–14 (0–3)	reported	reported	reported	reported	2–5 (1–3)	2–30 (2–4)	reported	nr
cariprazine (Vraylar)	15–29 (12)	reported	reported	nr	nr	7–8 (4)	2–3 (2)	1–10 (1–5)	nr
clozapine (Clozaril, Fazaclo, Versacloz)	1–4	reported	reported	9–13	nr	21–39	4	6–31	nr
iloperidone (Fanapt)	4–5 (4)	nr	reported	3–5 (1)	nr	9–15 (5)	1–9 (1)	nr	reported
lurasidone (Latuda)	11 (5)	reported	reported	0.4 (0.2)	reported	22 (10)	reported	2 (< 1)	nr
olanzapine oral (Zyprexa)	3–23 (1–13)	2.2–17.4 (3.4–11.5)	21.6–39.6 (9.5–26.1)	3–5 (1–2)	30–47 (7–10.5)	35–48 (9–13)	5–31 (1–9)	4–32 (0–9)	nr
olanzapine/fluoxetine (Symbyax)	< 1	0–37 (0.3–3.6)	8.2–67.8 (1.7–9.9)	4 (1.8)	28 (5)	14 (6)	22–66 (1.8–3)	15 (6)	reported
paliperidone ER (Invega)	3–20 (4–8)	reported	reported	1–4 (1)	reported	6–12 (5–7)	4–9 (1–5)	1–5 (1–2)	reported
pimavanserin (Nuplazid)§	nr	nr	nr	nr	nr	reported	nr	nr	reported
quetiapine (Seroquel)	3–12 (1–16)	10.7 (4.6)	4–22 (2–19)	3–7 (1–2)	3.6–13.4 (0–2.6)	18–57 (8–15)	5–23 (0–7)	7–44 (0–13)	reported

Adverse effects are reported as a percentage. Adverse effects are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

† Symptoms of skin irritation at the site of the Mycite patch may occur in some patients (12.4% in clinical trials).

§ Most notable adverse reactions with pimavanserin (Nuplazid) are peripheral edema and confusion. Urticaria- and angioedema-like reactions have been reported.

Adverse Effects (continued)

Drug	EPS	Glucose Abnormalities	Dyslipidemia	Hypotension	Prolactin Elevation	Sedation	Weight Gain	Anticholinergic Effects	QT Prolongation
Second Generation Antipsychotics – Oral *(continued)*									
quetiapine ER (Seroquel XR)	4–8 (1–5)	7–12 (6)	4–22 (2-19)	3–7 (0-5)	reported	5–14 (4)	1–10 (0–5)	6–40 (1–8)	reported
risperidone oral (Risperdal)	0–18 (0–7)	reported	reported	1–2 (0)	reported	12–67 (4–23)	18 (9)	4–21 (1–8)	reported
ziprasidone oral (Geodon)	14–31 (7–12)	reported	reported	reported	reported	14 (7)	5.6–10 (5.6–4)	4–9 (2–8)	reported
Second Generation Antipsychotics – Injectable*									
aripiprazole ER (Abilify Maintena)‖	5 (3)	reported	reported	nr	nr	7 (4)	reported	nr	nr
aripiprazole lauroxil ER¶ (Aristada, Aristada Initio)	5–7 (4)	nr	nr	nr	nr	nr	2 (1)	nr	nr
olanzapine IM (Zyprexa)	1–4 (0)	nr	nr	5	nr	6 (3)	nr	0-2	nr
olanzapine IM (Zyprexa Relprevv)	> 5	nr	6.5–24.5	nr	reported	8–13 (7)	5–7 (5)	2–6 (1)	2 (1)
paliperidone palmitate (Invega Sustenna)	0–5 (1)	reported	reported	reported	reported	1–7 (3)	1–4 (1)	reported	reported
paliperidone palmitate (Invega Trinza)	3–6 (1–3)	reported	reported	reported	reported	reported	9.6 (0.7)	reported	reported
risperidone ER microspheres (Risperdal Consta)	4–24 (3–16)	reported	reported	1–2 (0)	< 2	5–7 (1–3)	4–7 (1–2)	0–7 (1)	reported
risperidone ER suspension (Perseris)	1.7–4.3 (0.8)	reported	reported	reported	reported	7–7.7 (0)	12.8–13 (3.4)	reported	reported
ziprasidone IM (Geodon)	0–2	reported	nr	0–5	reported	8–20	nr	nr	nr

Adverse effects are reported as a percentage. Adverse effects are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

* Injection site reactions have been reported with injectable agents.

‡ Application site reactions (e.g., blisters, ulcers) have been reported with asenapine (Saphris).

‖ Most notable adverse reaction for Abilify Maintena was akathisia (8%).

¶ Most notable adverse reaction for Aristada was akathisia (11%).

Metabolic Effects

Of the second generation antipsychotics (SGAs), clozapine and olanzapine are the agents most frequently associated with weight gain and glucose and lipid abnormalities at therapeutic doses. In a case-control study of 93 patients who were receiving clozapine for schizophrenia or schizoaffective disorder, the prevalence of metabolic syndrome was 54% compared to 21% in the reference group.[334] These adverse effects occur with risperidone and quetiapine, but at a lower frequency than with olanzapine and clozapine. Ziprasidone and aripiprazole have the lowest incidence of these adverse effects.[335,336] These effects can be particularly problematic in patients with schizophrenia as they are likely to have other cardiovascular risk factors, such as smoking, sedentary lifestyle, and unhealthy diet.[337] The relative metabolic effects, including the development of diabetes, of the various SGAs have been demonstrated in several direct comparative clinical trials, prospective studies, and retrospective studies.

The effect of risperidone and olanzapine on body weight and body mass index (BMI) was observed prospectively over a 6-month period.[338] Significant increases in weight and BMI were apparent in both groups after 3 months of treatment ($p<0.05$). Significant increases in weight continued in both groups throughout the 6-month study, although there was significantly greater weight gain with olanzapine.

In a retrospective chart review of 215 patients taking clozapine, olanzapine, risperidone, quetiapine, haloperidol, or fluphenazine, glucose and lipid levels were evaluated from 2.5 years before and after initiation of the antipsychotic.[339] Glucose levels were increased from baseline for patients treated with clozapine, olanzapine, and haloperidol. All the medications demonstrated statistically significant changes in lipid profile ($p<0.05$), with patients receiving clozapine and olanzapine demonstrating the greatest increase in triglyceride levels.

Another study using Veterans Administration data evaluated patients with schizophrenia on antipsychotic monotherapy who developed diabetes or were hospitalized for ketoacidosis.[340] Of the 56,849 patients identified, 4,132 patients (7.3%) developed diabetes, and 88 patients (0.2%) were hospitalized for ketoacidosis. Clozapine followed by olanzapine demonstrated the highest risk for developing diabetes with hazard ratios of 1.57 and 1.15, respectively, while the risk of developing diabetes risk for quetiapine and risperidone were not significantly different from that for first generation antipsychotics (FGAs), hazard ratios of 1.2 and 1.01, respectively. The study demonstrated the risk of developing diabetes mellitus ranged from 0.05% (risperidone) to 2.03% (clozapine) for patients using SGAs. Though the study demonstrated a small risk to patients taking SGAs, patients with co-morbidities that may add to the risk of developing diabetes should receive periodic monitoring.

Investigators studied 101 patients with schizophrenia or schizoaffective disorder receiving clozapine.[341] In the patient group, the prevalence of diabetes was 25.7%. Mean duration of clozapine treatment was 5.7 years. Logistic regression of the data demonstrated a significant association between diabetes prevalence and Caucasian race ($p=0.02$), and the association between diabetes and family history of diabetes ($p=0.002$); however, significant associations were not demonstrated among diabetes prevalence and BMI or body fat.

A retrospective cohort study compared a cohort of patients with prescription claims for SGAs with a control cohort receiving FGAs, antidepressants, or antibiotics.[342] Investigators found an unadjusted incidence rate for diabetes (new cases per 1,000 per year) of 7.5 for second generation antipsychotics compared to 11.3 for first generation antipsychotics, 7.8 for antidepressants, and 5.1 for antibiotics.

The differences among the 3 groups of psychotropic agents were not statistically significant. A further comparison showed the risk of developing diabetes similar in patients receiving clozapine, olanzapine, ziprasidone, thioridazine, and risperidone.

Investigators studied 15,767 Veterans Health Administration patients with schizophrenia who started treatment with olanzapine, quetiapine, risperidone, or haloperidol over a 2-year period.[343] In an adjusted analysis of a follow-up after 1 year, each of the SGAs increased the risk of diabetes by 60 to 70% compared to haloperidol. The hazard ratio (HR) for risk of diabetes for olanzapine was 1.6 (95% confidence interval [CI], 1.2 to 2.2), for quetiapine was 1.7 (95%, CI 1 to 2.8), and for risperidone was 1.6 (95% CI, 1.2 to 2.1). The risk of diabetes was higher in patients younger than 50 years of age, as well as for patients receiving olanzapine, quetiapine, or risperidone treatment.

In a similar retrospective review of managed care claims for patients with bipolar disorder, 920 cases of new onset diabetes were case-matched with 5,258 controls.[344] Of the 920 cases, 41% received SGAs, and 34% received FGAs. Compared to FGAs, the HR for risk of diabetes among patients taking clozapine was 7 (95% CI, 1.7 to 28.9), for olanzapine was 3.2 (95% CI, 2.7 to 3.8), for quetiapine was 1.8 (95% CI, 1.4 to 2.4), and for risperidone was 3.4 (95% CI, 2.8 to 4.2). These results demonstrate an increased risk of new onset diabetes for patients receiving clozapine, olanzapine, quetiapine, and risperidone.

Adverse metabolic effects of the SGAs have been documented in the pediatric population. Recent literature reviews suggest that significant weight gain may occur in 50% to 60% of children treated with SGAs, and this patient group may be particularly susceptible to developing type 2 diabetes.[345,346] In a blinded, randomized, controlled trial of 39 children, ages 10 to 17 years, SGA-induced weight gain was virtually eliminated by concurrent administration of metformin.[347]

Furthermore, medical records (from 1996 through 2007) of Tennessee Medicaid patients ages 6 to 24 were examined in a large, retrospective study.[348] The cohort included 28,858 children and youth who had recently initiated antipsychotic therapy. The study showed patients on atypical antipsychotics risperidone, quetiapine, aripiprazole, and olanzapine had a 3-fold increased risk of developing type 2 diabetes within the first year of taking these drugs than did propensity score-matched controls (HR=2.49; 95% CI, 1.27 to 4.88). The risk of type 2 diabetes increased with cumulative dose.

SPECIAL POPULATIONS[349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392]

Pediatrics

Molindone, perphenazine, and thiothixene are not recommended in children < 12 years. Trifluoperazine is indicated for the treatment of schizophrenia in children ≥ 6 years old. Oral haloperidol may be used in patients ≥ 3 years of age, but safety and effectiveness of haloperidol lactate and haloperidol decanoate have not been established in pediatric patients. Pimozide (Orap) and thioridazine should not be used in patients < 2 years of age. Chlorpromazine is not for use in children < 6 months. Amitriptyline/perphenazine, fluphenazine, fluphenazine decanoate, fluphenazine HCl, oral loxapine, and loxapine inhalation powder (Adasuve) are not approved for use in pediatric patients.

Second generation antipsychotics are not intended for use in the pediatric patient who exhibit symptoms secondary to environmental factors and/or primary psychiatric disorders other than schizophrenia and bipolar disorder.

Aripiprazole oral (Abilify) is approved for treatment of schizophrenia in adolescents aged 13 to 17 years of age. Aripiprazole oral is also indicated as adjunctive or monotherapy for treatment of acute manic or mixed episodes associated with bipolar I disorder and maintenance of bipolar I disorder in pediatric patients aged 10 to 17 years, for treatment of irritability associated with autistic disorder in children and adolescents aged 6 to 17 years of age, and for treatment of Tourette's disorder in patients ages 6 to 18 years.

Asenapine (Saphris) is approved as monotherapy for the acute treatment of manic and mixed episodes in patients ≥ 10 years.

Lurasidone (Latuda) is approved for treatment of schizophrenia in adolescents aged 13 to 17 years of age and for the treatment of depressive episodes associated with bipolar I disorder in patients 10 to 17 years as monotherapy.

Olanzapine (Zyprexa) is approved for treatment of schizophrenia in adolescents aged 13 to 17 years of age and in adolescents aged 13 to 17 years for the treatment of acute manic or mixed episodes associated with bipolar I disorder and the maintenance treatment of bipolar I disorder. Compared to adults, adolescents taking olanzapine experienced a greater incidence of adverse effects. Olanzapine (Zyprexa) is approved in patients ≥ 10 years of age for the treatment of depressive episodes of bipolar disorder in combination with fluoxetine (Prozac) or as the fixed-dose combination of olanzapine/fluoxetine (Symbyax).

Paliperidone (Invega) is approved for treatment of schizophrenia in adolescents 12 to 17 years of age.

Quetiapine (Seroquel, Seroquel XR) is approved for treatment of schizophrenia in adolescents 13 to 17 years of age and for treatment of mania associated with bipolar disorder in patients 10 to 17 years of age. Quetiapine ER (Seroquel XR) is also approved for the treatment of mixed episodes in patients 10 to 17 years of age.

Oral risperidone (Risperdal) is approved for treatment of schizophrenia in adolescents aged 13 to 17 years of age, as monotherapy in children and adolescents aged 10 to 17 years for the treatment of acute manic or mixed episodes associated with bipolar I disorder, and for treatment of irritability associated with autistic disorder in children and adolescents aged 5 to 17 years of age.

Safety and effectiveness of aripiprazole tablets with sensor (Abilify Mycite), brexpiprazole (Rexulti), cariprazine (Vraylar), clozapine (Clozaril, Fazaclo, Versacloz), iloperidone (Fanapt), pimavanserin (Nuplazid), ziprasidone (Geodon), and the injectable SGA products in pediatric patients have not been established.

In 2011, AACAP published a Practice Parameter regarding the general use of SGAs in children and adolescents.[393] General recommendations address safety, recommend monitoring for efficacy and safety, emphasize evidence-based treatment, advise use of the lowest effective dose, and recommend against polypharmacy except in select cases (including multiple antipsychotics).

Pregnancy

Clozapine and lurasidone are Pregnancy Category B. All other antipsychotics assigned a Pregnancy Category are Pregnancy Category C. Aripiprazole lauroxil (Aristada, Aristada Initio), brexpiprazole (Rexulti), cariprazine (Vraylar), paliperidone (Invega Trinza), and pimavanserin (Nuplazid) have not been assigned a Pregnancy Category in compliance with the Pregnancy and Lactation Labeling Rule (PLLR); however, as with all medications, a risk versus benefit evaluation should be made between the

provider and patient prior to initiating 1 of these agents. The labels for asenapine (Saphris), iloperidone (Fanapt), paliperidone (Invega, Invega Sustenna), risperidone (Risperdal), and risperidone microspheres (Risperdal Consta), previously assigned Pregnancy Category C, now contain descriptive text in compliance with the PLLR. Data are limited on the use of these agents in pregnancy to completely inform of a drug-associated risk for major birth defects and miscarriage, although the limited available data from published studies have not established a drug-associated risk. A risk versus benefit evaluation should be conducted prior to initiating any of these agents.

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery.[394] There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while, in some cases, symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization. These products should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The major active metabolite of cariprazine (Vraylar), DDCAR, has been detected in adult patients up to 12 weeks after discontinuation of the product.

Healthcare providers are encouraged to register pregnant women in the pregnancy exposure registry who are treated with the following SGAs: aripiprazole (Abilify, Abilify Mycite, Abilify Maintena, Abilify Mycite, Aristada, Aristada Initio), asenapine (Saphris), brexpiprazole (Rexulti), cariprazine (Vraylar), lurasidone (Latuda), paliperidone palmitate (Invega Trinza), and risperidone (Perseris, Risperdal, Risperdal Consta).

Geriatrics

Elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo when treated with any antipsychotic. The cause of reported death in elderly patients treated with SGAs varies. Most deaths appeared to be either cardiovascular- or infection-related.

Cerebrovascular adverse reactions, including stroke, have been reported in elderly patients with dementia treated with SGAs.

Medications with significant anticholinergic effects may increase cognitive impairment, falls, and all-cause mortality, particularly when used in combination with other medications with anticholinergic effects.[395] The American Geriatrics Society (AGS) includes all antipsychotics on their Beers Criteria of potentially inappropriate medications in older adults, stating that they should be avoided except for schizophrenia, bipolar disorder, or short-term use as an antiemetic during chemotherapy.[396] This is due to the increased risk of mortality in patients treated with antipsychotics for dementia-related psychosis and greater rate of cognitive decline in this population. They further state that antipsychotics should be avoided for behavioral problems of dementia or delirium unless nonpharmacologic options have failed and there is a threat of harm to self or others. They recommend quetiapine, clozapine, and pimavanserin as exceptions to the general avoidance guidance. Specifically for treating psychosis in patients with Parkinson's disease, aripiprazole has been removed from the preferred medications and replaced with pimavanserin. The panel cautions that there are safety and efficacy concerns for all antipsychotics in older adults.

Hepatic Impairment

Asenapine (Saphris) is contraindicated in patients with severe hepatic impairment (Child-Pugh class C), but no dosage adjustment is required in mild to moderate hepatic impairment.

Patients with moderate to severe hepatic impairment (Child-Pugh class B or C) experienced higher exposure to brexpiprazole (Rexulti) than patients with normal hepatic function. The maximum recommended dosage should be reduced in patients with moderate to severe hepatic impairment.

No dosage adjustment of cariprazine (Vraylar) is required in patients with mild to moderate hepatic impairment (Child-Pugh Class A or B). Cariprazine is not recommended for patients with severe hepatic impairment as its use in this population has not been evaluated.

Caution is recommended in patients using clozapine (Clozaril, Fazaclo, Versacloz) who have concurrent hepatic disease. Hepatitis has been reported in both patients with normal and pre-existing liver function abnormalities. Liver function tests should be performed immediately in patients on clozapine who develop nausea, vomiting, and/or anorexia. Treatment should be discontinued if elevation of these values is clinically relevant or if symptoms of jaundice occur.

Studies of haloperidol in patients with hepatic impairment have not been conducted; however, concentrations of haloperidol in hepatically impaired patients may be increased as it is primarily metabolized by the liver.

For mild hepatic impairment, no dose adjustment is required with iloperidone (Fanapt). For moderate hepatic impairment, caution should be exercised. Iloperidone is not recommended in patients with severe hepatic impairment.

Dosing of lurasidone (Latuda) should not exceed more than 80 mg and 40 mg daily in patients with moderate or severe hepatic impairment, respectively.

Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of olanzapine/fluoxetine (Symbyax) may be altered in patients with hepatic impairment.

Paliperidone ER (Invega) has not been studied in severe hepatic impairment. No dosage adjustment of oral paliperidone is recommended in mild to moderate hepatic impairment. Paliperidone palmitate (Invega Sustenna, Invega Trinza) has not been studied in patients with hepatic impairment.

No dosage adjustment is recommended for pimavanserin (Nuplazid) in patients with hepatic impairment.

Since quetiapine (Seroquel, Seroquel XR) is extensively metabolized by the liver, higher plasma levels are expected in hepatic-impaired patients, and dosage adjustment may be needed.

Risperidone (Risperdal) doses should be decreased in patients with hepatic disease. Doses of injectable risperidone (Risperdal Consta) in this population should be based on oral risperidone dosing. Patients prescribed SC risperidone (Perseris) who have hepatic impairment, should be carefully titrated with oral risperidone, up to at least 3 mg, prior to starting SC risperidone at a dose of 90 mg.

Liver impairment may decrease clearance of ziprasidone (Geodon); monitor as clinically indicated and adjust dose if necessary.

Renal Impairment

Patients with impaired renal function experienced higher exposure to brexpiprazole (Rexulti) than patients with normal renal function. The maximum recommended dosage should be reduced in patients with moderate, severe, or end-stage renal impairment (ESRD) (creatinine clearance [CrCl] < 60 mL/minute).

No dosage adjustment of cariprazine (Vraylar) is required in patients with mild to moderate renal impairment (CrCl ≥ 30 mL/min). Cariprazine is not recommended for patients with severe renal impairment (CrCl < 30 mL/min) as its use in this population has not been evaluated.

Caution is recommended in patients using clozapine (Clozaril, Fazaclo, Versacloz) who have renal impairment; a dose reduction may be necessary.

Dosing of lurasidone (Latuda) should not exceed 80 mg daily in patients with moderate or severe renal impairment.

Dosing for paliperidone (Invega, Invega Sustenna, Invega Trinza) must be individualized according to renal function status. The use of paliperidone palmitate (Invega Sustenna, Invega Trinza) is not recommended in patients with moderate to severe renal impairment (CrCl < 50 mL/min).

No dose adjustment of pimavanserin (Nuplazid) is needed in those with mild to severe renal impairment or ESRD. Increased exposure has occurred in those with severe renal impairment or ESRD; it should be used cautiously in these populations.

Risperidone (Risperdal) doses should be decreased in patients with renal disease. Doses of injectable risperidone (Risperdal Consta) in this population should be based on oral risperidone dosing. Patients prescribed SC risperidone (Perseris) who have renal impairment, should be carefully titrated with oral risperidone, up to at least 3 mg, prior to starting SC risperidone at a dose of 90 mg.

Smoking

Tobacco smoke may decrease clozapine (Clozaril, Fazaclo, Versacloz) plasma levels, most likely related to the effect on CYP1A2, resulting in a decrease in effectiveness of a previously effective dose. Olanzapine clearance is approximately 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely recommended. Some evidence suggests that tobacco smoke also increases the rate of metabolism of phenothiazine antipsychotics, such as fluphenazine decanoate. Sudden discontinuation of tobacco smoking may lead to reduced clearance of these agents, regardless if nicotine replacement occurs.

Other

A disproportionate number of cases of clozapine-related agranulocytosis in patients of Jewish descent have been reported.

Benign ethnic neutropenia (BEN), which may be referred to as familial neutropenia, constitutional neutropenia, or benign familial leukopenia, is an inherited neutropenia that occurs in select individuals and ethnic groups (e.g., African descent, Jewish descent, Arab descent). In general, the neutropenia is considered mild but is lower than standard reference ranges. Notably, patients with BEN are not at a higher risk for clozapine-induced neutropenia. The clozapine REMS program provides guidance for dosing considerations and monitoring in this population.[397]

DOSAGES[398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442]

Adults

Drug	Schizophrenia/Psychotic Disorders		Other Indications	Dosage Forms
	Initial Dose	Usual Maintenance Dose		
First Generation Antipsychotics				
amitriptyline/ perphenazine	25/2 mg to 50/8 mg 3 to 4 times daily	Stable dose 2 to 4 times daily	--	Tablets: 10/2 mg, 10/4 mg, 25/2 mg, 25/4 mg, 50/4 mg
chlorpromazine	Oral: 25 mg 3 times daily IM: ≤ 25 mg x 1 dose, may repeat as 25 mg to 50 mg as needed hourly	Oral: up to 1,000 mg daily IM: 300 mg to 800 mg per day (divided) every 4 to 6 hours	Oral: 25 to 100 mg 3 or 4 times daily IM: 12.5 to 50 mg every 3-8 hours	Tablets: 10 mg, 25 mg, 50 mg, 100 mg, 200 mg Vials for injection: 25 mg/mL
fluphenazine	Oral: 2.5 mg to 10 mg 3 to 4 times daily IM (hydrochloride): 1.35 mg every 6 to 8 hours IM/SC (decanoate): 12.5 mg to 25 mg, injection may control symptoms for 4 to 6 weeks	Oral: 1 mg to 5 mg daily IM (hydrochloride): 2.5 mg to 10 mg per day (divided) every 6 to 8 hours IM/SC (decanoate): 50 mg every 1 to 4 weeks as needed/tolerated	--	Tablets: 1 mg, 2.5 mg, 5 mg, 10 mg Elixir: 2.5 mg/5 mL Concentrate: 5 mg/mL Vials for injection: 2.5 mg/mL (hydrochloride), 125 mg/5 mL (decanoate)
haloperidol (Haldol)	Oral: 0.5 mg to 2 mg 2 to 3 times daily IM (lactate): 2 mg to 5 mg every 4 to 8 hours (up to every 1 hour; maximum dose: 20 mg/day IM (decanoate): 10 to 15 times the oral daily dose, generally every 4 weeks (maximum: 450 mg/month)	Up to 100 mg daily for tablets and elixir; 20 mg daily for lactate injection; 450 mg per month for decanoate	0.5 to 1.5 mg 3 times daily (Tourette's); 0.05 to 0.075 mg/kg/day (behavioral disorders, hyperactivity)	Tablets†: 0.5 mg, 1 mg, 2 mg, 5 mg, 10 mg, 20 mg Elixir/concentrate†: 2 mg/mL Ampules/vials/syringe for injection: 5 mg/mL (lactate); Ampules/vials for injection 50 mg/mL, 100 mg/mL (decanoate)
loxapine	10 mg twice daily	60 mg to 100 mg divided into 2 to 4 doses daily	--	Capsules: 5 mg, 10 mg, 25 mg, 50 mg
loxapine inhalation powder (Adasuve)	Oral inhalation: 10 mg; only 1 dose should be administered within a 24-hour period*			Single-use inhaler: 10 mg
molindone	50 mg to 75 mg in 3 to 4 divided doses	5 mg to 25 mg 3 to 4 times daily, up to 225 mg daily	--	Tablets: 5 mg, 10 mg, 25 mg
perphenazine	4 mg to 8 mg 3 times daily	Up to 64 mg daily	--	Tablets: 2 mg, 4 mg, 8 mg, 16 mg
pimozide (Orap)	--	--	0.2 mg/kg/day for Tourette's	Tablets: 1 mg, 2 mg
thioridazine	50 mg to 100 mg 3 times daily	Up to 800 mg daily	--	Tablets: 10 mg, 25 mg, 50 mg, 100 mg
thiothixene	2 mg 3 times daily	Up to 60 mg daily	--	Capsules: 1 mg, 2 mg, 5 mg, 10 mg
trifluoperazine	2 mg to 5 mg twice daily	15 mg to 20 mg daily	1 to 2 mg twice daily (non-psychotic anxiety)	Tablets: 1 mg, 2 mg, 5 mg, 10 mg

* Loxapine inhalation powder (Adasuve) should be administered by a healthcare professional.
† Available as generic only.

Dosages – Adults

Drug	Other Indications	Schizophrenia		Bipolar Disorder		Dosage Forms
		Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose	
Second Generation Antipsychotics						
aripiprazole (Abilify, Abilify Maintena; Abilify Mycite)	Adjunctive treatment for depression: 2 mg to 5 mg daily, maintenance dose 5 mg to 10 mg daily (maximum dose: 15 mg daily) Tourette's disorder: < 50 kg: initial dose 2 mg daily, maintenance dose 5 mg daily (maximum dose 10 mg daily) ≥ 50 kg: initial dose 2 mg daily, maintenance dose 10 mg daily (maximum dose 20 mg daily)	Oral: 10 mg to 15 mg once daily IM: 9.75 mg (maximum dose = 30 mg daily) IM (Maintena): 400 mg monthly	10 mg to 15 mg once daily (maximum dose = 30 mg daily) IM (Maintena): 400 mg IM once monthly based upon tolerability	15 mg once daily IM: 9.75 mg (maximum dose = 30 mg daily) 10 mg to 15 mg once daily (adjunct to lithium and valproate)	15 mg once daily Maximum dose = 30 mg/day IM (Maintena): 400 mg monthly	Tablets: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg Orally disintegrating tablets†: 10 mg, 15 mg Oral solution†: 1 mg/mL Mycite tablets with sensor kit‡: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg Maintena extended-release suspension in syringes and lyophilized powder in vials for injection: 300 mg and 400 mg and suspension
aripiprazole lauroxil ER (Aristada)	--	441 mg, 662 mg, or 882 mg monthly, 882 mg every 6 weeks, or 1,064 mg every 2 months	441 mg, 662 mg, or 882 mg monthly, 882 mg every 6 weeks, or 1,064 mg every 2 months	--	--	Extended-release suspension for injection in syringes: 441 mg/1.6 mL, 662 mg/2.4 mL, 882 mg/3.2 mL, 1,064 mg/3.9 mL
aripiprazole lauroxil ER (Aristada Initio)	--	One 675 mg dose (plus a single oral aripiprazole 30 mg dose in conjunction with the first Aristada injection); it is not intended for repeat dosing	--	--	--	Extended-release suspension for injection in syringe: 675 mg/2.4 mL

† Available as generic only.

‡ Abilify Mycite kit contains a Mycite patch, a wearable sensor that detects the tablet sensor following ingestion, and is intended for use with the Mycite smartphone app and a web-based portal for use by caregivers and healthcare providers.

Dosages – Adults (continued)

Drug	Other Indications	Schizophrenia		Bipolar Disorder		Dosage Forms
		Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose	
Second Generation Antipsychotics *(continued)*						
asenapine (Saphris)	--	Acute: 5 mg twice daily Maintenance: 5 mg twice daily	Acute: 5 mg twice daily Maximum dose = 10 mg twice daily Maintenance: 10 mg twice daily Maximum dose = 10 mg twice daily	Acute: 10 mg twice daily as monotherapy 5 mg twice daily (adjunct to lithium and valproate)	5 mg to 10 mg twice daily Maximum dose = 10 mg twice daily 5 mg to 10 mg twice daily (adjunct to lithium and valproate or monotherapy) Maximum dose = 10 mg twice daily	Sublingual tablets: 2.5 mg, 5 mg, 10 mg (black cherry flavor)
brexpiprazole (Rexulti)	Adjunctive treatment of major depressive disorder: starting 0.5 mg or 1 mg once daily, target dose 2 mg once daily, maximum 3 mg daily	1 mg once daily on Days 1 to 4	2 mg to 4 mg once daily Maximum dose = 4 mg daily	--	--	Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg
cariprazine (Vraylar)	--	1.5 mg once daily; may be increased to 3 mg by Day 2	1.5 mg to 6 mg once daily	1.5 mg once daily; may be increased to 3 mg by Day 2	3 mg to 6 mg once daily	Capsules: 1.5 mg, 3 mg, 4.5 mg, 6 mg Titration pack: one 1.5 mg and six 3 mg capsules
clozapine (Clozaril)	--	12.5 mg once or twice daily	Target: 300 to 450 mg/day Maximum dose= 900 mg/day	--	--	Tablets: 25 mg, 50 mg†, 100 mg, 200 mg†
clozapine (Fazaclo)						ODT: 12.5 mg, 25 mg, 100 mg, 150 mg, 200 mg
clozapine (Versacloz)						Suspension: 50 mg/mL

† Available as generic only.

Dosages – Adults (continued)

Drug	Other Indications	Schizophrenia		Bipolar Disorder		Dosage Forms
		Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose	
Second Generation Antipsychotics *(continued)*						
iloperidone (Fanapt)	--	1 mg twice daily	12 mg to 24 mg twice daily	--	--	Tablets: 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg Titration pack: 8 tablets with 2 tablets each of 1 mg, 2 mg, 4 mg, and 6 mg
lurasidone (Latuda)	--	40 mg once daily with food	40 mg to 160 mg once daily with food Maximum dose = 160 mg/day	20 mg once daily with food	20 mg to 120 mg once daily with food Maximum dose = 160 mg/day	Tablets: 20 mg, 40 mg, 60 mg, 80 mg, 120 mg
olanzapine (Zyprexa, Zyprexa Relprevv)	--	5 mg to 10 mg once daily IM (short-acting): 2.5 mg to 10 mg IM (long-acting): 150 mg to 300 mg every 2 weeks or 405 mg every 4 weeks	10 mg once daily IM (short-acting): up to 30 mg daily IM (long-acting): after 8 weeks, 150 mg to 300 mg every 2 weeks or 300 mg to 405 mg every 4 weeks	Manic or mixed: 10 mg to 15 mg once daily IM (short-acting): 2.5 mg to 10 mg	Manic or mixed: 5 mg to 20 mg once daily IM (short-acting): Up to 30 mg daily	Tablets: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg ODT: 5 mg, 10 mg, 15 mg, 20 mg Immediate release vial for injection: 10 mg Relprevv extended-release vial for injection and as a kit containing diluent and syringes: 210 mg, 300 mg, 405 mg
olanzapine/ fluoxetine (Symbyax)	Treatment-resistant depression: 6/25 mg daily in evening	--	--	6/25 mg daily in evening	6/25 mg to 12/50 mg daily in evening	Capsules: 3/25 mg, 6/25 mg, 6/50 mg, 12/25 mg§, 12/50 mg

§ The 12/25 mg strength of Symbyax by Eli Lilly has been discontinued; some supply may remain until stock is depleted.

Dosages – Adults (continued)

Drug	Other Indications	Schizophrenia		Bipolar Disorder		Dosage Forms
		Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose	
Second Generation Antipsychotics *(continued)*						
paliperidone ER (Invega) paliperidone palmitate (Invega Sustenna, Invega Trinza)	Schizoaffective disorder: initial 6 mg/day, maintenance 3 to 12 mg/day (maximum 12 mg/day) IM (Invega Sustenna): initial 234 mg/day on day 1 then 156 mg/day on day 8, maintenance 78 to 234 mg/day (maximum 234 mg/day)	6 mg once daily Invega Sustenna IM: 234 mg IM on day 1, then 156 mg IM 1 week later IM (Invega Trinza): once every 3 months; dose dependent upon previous dose of Invega Sustenna	3 mg to 12 mg once daily (maximum dose = 12mg/day) Invega Sustenna IM: 117 mg monthly (range 39 mg to 234 mg)	--	--	Tablets: 1.5 mg, 3 mg, 6 mg, 9 mg Sustenna extended-release injection: 39 mg, 78 mg, 117 mg, 156 mg, 234 mg Trinza extended-release injection: 273 mg, 410 mg, 546 mg, 819 mg
pimavanserin (Nuplazid)¶	Psychosis associated with Parkinson's disease: 34 mg once daily	--	--	--	--	Tablets: 10 mg, 17 mg Capsule: 34 mg
quetiapine (Seroquel)	Bipolar depression Initial 50 mg/day, maintenance 300 mg/day, maximum 300 mg/day	25 mg twice daily	150 to 750 mg/day; divided into 2 to 3 doses	50 mg twice daily	400 to 800 mg/day	Tablets: 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg
quetiapine ER (Seroquel XR)	Major depressive disorder in combination with antidepressants: initial 50 mg/day, recommended 150 to 300 mg/day Depressive episodes associated with bipolar disorder: initial 100 mg/day, recommended 300 mg/day	300 mg in the evening	400 to 800 mg/day	300 mg in the evening	400 to 800 mg/day	ER tablets: 50 mg, 150 mg, 200 mg, 300 mg, 400 mg

¶ Available through specialty pharmacies. Pimavanserin (Nuplazid) 34 mg capsules were approved in June 2018, at which time the 17 mg tablet was discontinued; the 17 mg tablet may remain available until supply is depleted.

Dosages – Adults (continued)

Drug	Other Indications	Schizophrenia		Bipolar Disorder		Dosage Forms
		Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose	
Second Generation Antipsychotics *(continued)*						
risperidone (Perseris)	--	90 mg or 120 mg SC once monthly	90 mg or 120 mg SC once monthly	--	--	ER injection: 90 mg, 120 mg
risperidone (Risperdal, Risperdal Consta)	--	2 mg/day (in 1 to 2 divided doses) IM (Risperdal Consta): 25 mg every 2 weeks	4 to 8 mg/day (range, 4 to 16 mg/day) IM (Risperdal Consta): 25 mg to 50 mg every 2 weeks	2 mg to 3 mg once daily IM (Risperdal Consta): 25 mg every 2 weeks	1 to 6 mg/day IM (Risperdal Consta): 25 mg to 50 mg every 2 weeks	Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg ODT†: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg Oral solution: 1 mg/mL Consta ER injection: 12.5 mg, 25 mg, 37.5 mg, 50 mg
ziprasidone (Geodon)	--	20 mg twice IM: 10 to 20 mg	40 mg to 80 mg twice daily IM: Up to 40 mg daily for 3 consecutive days	40 mg twice daily	40 mg to 80 mg twice daily	Capsules: 20 mg, 40 mg, 60 mg, 80 mg Vial: 20 mg

† Available as generic only.

Pediatrics

Drug	Other Indications	Schizophrenia		Bipolar Disorder	
		Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose
First Generation Antipsychotics					
chlorpromazine	0.5 mg/kg 2 to 3 hours before operation (preoperative apprehension); 0.5 mg/kg every 4 to 6 hours as needed (N/V); 0.5 mg/kg every 4 to 6 hours (severe behavioral problems)	--	--	--	--
haloperidol	0.05 to 0.075 mg/kg/day (Tourette's disorder, non-psychotic behavior disorders/hyperactivity)	0.5 mg daily	0.15 mg/kg/day in divided doses	--	--
molindone	--	See adult dosing	See adult dosing	--	--
perphenazine	See adult dosing (N/V)	See adult dosing	See adult dosing	--	--
pimozide (Orap)	0.05 mg/kg/day up to 0.2 mg/kg/day (Tourette's disorder)*	--	--	--	--
thioridazine	--	0.5 mg/kg/day in divided doses	3 mg/kg/day in divided doses	--	--
thiothixene	--	See adult dosing	See adult dosing	--	--
trifluoperazine	--	1 mg once or twice daily†	Up to 15 mg daily†	--	--
Second Generation Antipsychotics					
aripiprazole (Abilify)*	Age 6 to 17 years: 2 mg daily	Age 6 to 17 years: 5 mg to 10 mg daily Maximum dose = 15 mg daily	Age 13 to 17 years: 2 mg daily	Age 13 to 17 years: 10 mg daily Maximum dose = 30 mg daily	Age 10 to 17 years: 2 mg daily
asenapine (Saphris)	--	--	--	--	Age 10–17 years: 2.5 mg twice daily
lurasidone (Latuda)	--	Age 13 to 17 years: 40 mg once daily	Age 13 to 17 years: 40 mg to 80 mg daily	Age 10 to 17 years: 20 mg once daily	Age 10 to 17 years: 20 mg to 40 mg once daily (max 80 mg daily)
olanzapine (Zyprexa)†	--	--	Age 13 to 17 years: 2.5 mg to 5 mg daily	Age 13 to 17 years: 10 mg daily	Age 13 to 17 years: 2.5 mg to 5 mg daily

* CY2D6 genotyping should be performed prior to initiation; do not exceed 0.05 mg/kg/day in poor CYP2D6 metabolizers.

† Dosing for children ages 6 to 12 years old.

Dosages – Pediatrics (continued)

Drug	Irritability associated with Autistic Disorder		Schizophrenia		Bipolar Disorder	
	Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose
Second Generation Antipsychotics (continued)						
olanzapine/ fluoxetine (Symbyax)	--	--	--	--	Age 10 to 17 years: 3/25 mg daily	Age 10 to 17 years: 6/25 mg to 12/50 mg daily
paliperidone (Invega)	--	--	Age 12 to 17 years: Weight < 51 kg: 3 mg daily Weight ≥ 51 kg: 3 mg daily	Age 12 to 17 years: Weight < 51 kg: 3 mg to 6 mg daily Maximum dose = 6 mg daily Weight ≥ 51 kg: 3 mg to 12 mg daily Maximum dose = 12 mg daily	--	--
quetiapine (Seroquel)	--	--	Age 13 to 17 years: 25 mg twice daily	Age 13 to 17 years: 400 mg to 800 mg per day	Age 10 to 17 years: 25 mg twice daily	Age 10 to 17 years: 400 mg to 600 mg per day
quetiapine (Seroquel XR)	--	--	Age 13 to 17 years: 50 mg to 400 mg per day	Age 13 to 17 years: 400 mg to 800 mg per day	Age 10 to 17 years: 50 mg to 400 mg per day	Age 10 to 17 years: 400 mg to 600 mg per day
risperidone (Risperdal)	Age 5 to 17 years: Weight < 20 kg: 0.25 mg daily Weight ≥ 20 kg: 0.5 mg daily	Age 5 to 17 years: Weight < 20 kg: 0.5 mg daily after at least 4 days Weight ≥ 20 kg: 1 mg daily after at least 4 days Maintain for at least 14 days; If insufficient response, increase at ≥ 2 week intervals by 0.25 mg per day for weight < 20 kg or 0.5 mg per day for weight ≥ 20 kg (range, 0.5 to 3 mg/day)	Age 13 to 17 years: 0.5 mg daily	Age 13 to 17 years: 3 mg daily (range, 1 to 6 mg/day)	Age 10 to 17 years: 0.5 mg daily	Age 10 to 17 years: 1 mg to 2.5 mg daily (range, 1 to 6 mg/day)

*The efficacy of aripiprazole for the maintenance treatment of irritability associated with autistic disorder was not established. Patients should be periodically reassessed to determine the continued need for maintenance treatment. Aripiprazole (Abilify) is also approved for the treatment of Tourette's disorder. For this indication, the initial dose is 2

mg/day, regardless of weight. The recommended dose is 5 mg/day in patients < 50 kg (maximum dose, 10 mg/day) and 10 mg/day in patients ≥ 50 kg (maximum dose, 20 mg/day). Abilify Mycite is *not* approved for use in pediatric patients.

† Dosing in clinical trials ranged to 20 mg/day in schizophrenia and bipolar I disorder (manic and mixed episodes). The safety and effectiveness of olanzapine (Zyprexa) at doses above 20 mg have not been established. Olanzapine is also approved in combination with fluoxetine in children and adolescents 10 to 17 years of age; see olanzapine/fluoxetine (Symbyax) for details on dosing.

Dosing Considerations

Prior to administering loxapine inhalation powder (Adasuve), all patients should be screened for a history of pulmonary disease, and examined (including chest auscultation) for respiratory abnormalities (e.g., wheezing). After administration, patients should be monitored for signs and symptoms of bronchospasm. Again, a physical examination, including chest auscultation, should be performed at least every 15 minutes for at least 1 hour.

Aripiprazole tablets with sensor (Abilify Mycite) should be used with the Mycite patch, a wearable sensor that detects the tablet sensor following ingestion, the Mycite smartphone app, and a web-based portal for use by caregivers and healthcare providers. Tablets should be swallowed whole; do not divide, crush, or chew. Most ingestions will be detected within 30 minutes, but it may take up to 2 hours for the app and/or portal to detect the ingestion. In some cases, the ingestion may not be detected. The patch should be applied to the left side of the body just above the lower edge of the rib cage in areas where the skin is not scraped, cracked, inflamed, or irritated and should not overlap the area of the most recently removed patch. Patients should keep the patch on when showering, swimming, or exercising, but should change it weekly or sooner as needed. The MYCITE APP, smartphone application, will prompt the patient to change the patch and provides patch application instructions. Patients undergoing magnetic resonance imaging (MRI) should remove the patch and replace it with a new one once completed. If skin irritation occurs, the patient should remove the patch.

Asenapine (Saphris) sublingual tablets should not be swallowed; they should be placed under the tongue and left to dissolve completely. Patients taking asenapine (Saphris) should not ingest food or water for 10 minutes following a dose.

Prior to initiating clozapine products, a baseline absolute neutrophil count (ANC) must be obtained and should be monitored regularly thereafter. See prescribing information for appropriate dosing titration and dose tapering (for discontinuation) as well as monitoring details for ANC.

The dose of iloperidone (Fanapt) should be reduced by one-half for patients who are taking CYP2D6 or 3A4 inhibitors. Patients must be titrated to an effective dose of iloperidone; as a result, control of symptoms may be delayed 1 to 2 weeks with iloperidone compared to other antipsychotics not requiring a titration period.

Lurasidone (Latuda) and ziprasidone (Geodon) should be given with food. A snack or meal of at least 350 calories is recommended with lurasidone.

The starting dose of olanzapine/fluoxetine (3 mg/25 mg to 6 mg/25 mg) should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine/fluoxetine. These factors include female gender, geriatric age, non-smoking status, or those patients who may be pharmacodynamically sensitive to olanzapine. Dosing modification may be necessary in patients who

exhibit a combination of factors that may slow metabolism. When indicated, dose escalation should be performed with caution in these patients.

The dose of paliperidone ER (Invega) should be reduced in patients with moderate or severe renal impairment as its clearance is reduced by 64% to 71%. Dosing should be individualized in renally-impaired patients taking patients taking injectable formulations of paliperidone. The use of paliperidone palmitate (Invega Sustenna, Invega Trinza) is not recommended in patients with moderate to severe renal impairment (CrCl < 50 mL/min).

The recommended dose of pimavanserin (Nuplazid) dose is 10 mg once daily when coadministered with a strong CYP3A4 inhibitor (e.g., ketoconazole), and an increased dose may be warranted if used with a strong CYP3A4 inducer.

The initial quetiapine (Seroquel) dose should be 25 mg once daily in patients with hepatic impairment. For dosing of quetiapine ER (Seroquel XR) in patients with hepatic impairment, dosing begins at 50 mg daily. Quetiapine ER should be administered either without food or with a light meal.

The initial risperidone (Risperdal) dose should be reduced to 0.5 mg twice daily in patients who are elderly, debilitated, have severe renal or hepatic impairment, or are prone to hypotension and titrated appropriately. Dosing for these patients should be individualized based on comorbid condition. Similarly, dosing of risperidone injection (Perseris, Risperdal Consta) should also be individualized in patients with these comorbid conditions. In addition, oral risperidone doses should not exceed 8 mg in those taking select medications (e.g., fluoxetine, paroxetine) and dosing may need to be increased in patients using both CYP3A4 and P-gp inducers. These interactions should also be taken into consideration when the injectable formulation is used; see prescribing information for additional details.

Prior to initiating therapy with long-acting intramuscular antipsychotics, patients should be previously stabilized on short-acting formulations and should have tolerability established with oral agents. All long-acting agents in this review, except fluphenazine decanoate and risperidone ER (Perseris), are intended for deep IM injection, as administered by a healthcare professional (HCP). Fluphenazine decanoate may be given by IM or subcutaneous injection by a HCP. Risperidone ER (Perseris) is given only as an abdominal SC injection by a HCP. Administer of SGAs are intended as a single injection; do not divide into multiple injections.

In conjunction with the first dose of aripiprazole IM injection (Abilify Maintena), the patient should take 14 consecutive days of oral aripiprazole (10 mg to 20 mg) or other oral antipsychotic. Aripiprazole (Abilify Maintena) dosage may be reduced to 300 mg monthly in patients that experience adverse reactions. A dose decrease should be considered in patients who are CYP2D6 poor metabolizers. Concurrent administration of a CYP3A4 inducer should be avoided for more than 14 days. Recommended dosage adjustments are provided in the prescribing information when given concurrently with CYP3A4 or CYP2D6 inhibitors. If transitioning from another depot injection, administer Abilify Maintena in place of the next scheduled injection. No oral supplementation is required. See prescribing information for additional details on dosing, such as missed doses. Monthly doses should occur no sooner than every 26 days.

Aripiprazole lauroxil (Aristada) should only be administered in the deltoid (441 mg only) or gluteal muscle. Doses of 441 mg, 662 mg, and 882 mg aripiprazole lauroxil (Aristada) correspond to doses of 300 mg, 450 mg, and 600 mg of aripiprazole IM and 10 mg, 15 mg, and ≥ 20 mg/day of oral

aripiprazole, respectively. Doses of 882 mg every 6 weeks and 1,064 mg every 2 months correspond to 15 mg/day. Administer no sooner than 14 days after the previous injection; continue treatment with oral aripiprazole for 21 consecutive days to maintain therapeutic antipsychotic concentrations during initiation of therapy. Alternatively, treatment may be initiated with Aristada Initio, as described below. Avoid initiating Aristada with Aristada Initio in patients requiring dose adjustments. Prior to treatment with Aristada, aripiprazole tolerability should be established. Due to the half-life of oral aripiprazole, it may take up to 2 weeks to establish tolerability. See prescribing information for additional details on dosing, such as missed doses, and labeling for aripiprazole oral for any relevant dose adjustments during the initial 21 days.

The 675 mg strength aripiprazole lauroxil (Aristada Initio) is to be used as a single dose for initiation of long-term treatment with any dose of aripiprazole lauroxil (Aristada), or as a single dose to restart treatment after a missed dose of Aristada depending on the time since the last Aristada injection; it is not intended for repeat dosing. Administer a single oral aripiprazole 30 mg dose, a single Aristada Initio 675 mg dose**,** plus the first dose of Aristada based on the current oral aripiprazole dose with (or within 10 days following) the administration of the 675 mg dose**.** Aristada Initio should be injected IM in the deltoid or gluteal muscle by a healthcare professional; it is not recommended to inject Aristada Initio plus Aristada concurrently in the same muscle. Use caution when initiating Aristada and Aristada Initio due to the potential for substitution and dispensing errors. Refer to the Aristada Initio labeling for further dosing information.

Olanzapine ER (Zyprexa Relprevv) is intended for deep intramuscular gluteal injection only. Tolerability should be established with oral olanzapine prior to starting olanzapine ER injections. The recommended starting dose is of olanzapine ER 150 mg every 4 weeks in patients who may metabolize olanzapine more slowly, such as patients who are debilitated, predisposed to hypotensive reactions, or who may be more pharmacodynamically sensitive to olanzapine.

Paliperidone palmitate (Invega Sustenna and Invega Trinza) and risperidone microspheres (Risperdal Consta) are intended for intramuscular use into the deltoid or gluteal muscle. The first and second initiation doses of Invega Sustenna must be administered in the deltoid muscle; monthly maintenance doses can be administered in either the deltoid or gluteal muscle. Patients should be established on at least 4 monthly doses of Invega Sustenna before switching to Invega Trinza; Invega Trinza maintenance dose should be based on the last 2 Invega Sustenna doses. See prescribing information for additional details.

Oral risperidone (Risperdal) should be given with the first injection of risperidone microspheres (Risperdal Consta) and continued for 3 weeks. Dosing of risperidone (Risperdal Consta) should also be individualized in patients who are elderly, debilitated, have severe renal or hepatic impairment, or are prone to hypotension.

Risperidone SC injection (Perseris) 90 mg and 120 mg correspond to daily doses of 3 mg and 4 mg of oral risperidone, respectively. Patients who are on stable oral risperidone doses lower than 3 mg/day or higher than 4 mg/day may not be candidates for SC risperidone. No loading dose or supplemental oral risperidone is recommended prior to initiating risperidone SC injections. Patients with hepatic or renal impairment should be carefully titrate with oral risperidone, up to at least 3 mg, prior to starting SC risperidone at a dose of 90 mg.

If considering fluoxetine or paroxetine therapy concurrently with SC risperidone (Perseris), patients should be placed on the lowest dose of SC risperidone (90 mg) 2 to 4 weeks prior to starting the

antidepressant. If considering concurrent therapy with a strong CYP3A4 inducer (e.g., carbamazepine), the dose of SC risperidone should be increased to 120 mg in patients on 90 mg, or addition of oral risperidone should be considered if the patient is already on 120 mg. Likewise, with IM risperidone (Risperdal Consta), the dosage should be titrated as appropriate in patients starting on concurrent fluoxetine or paroxetine.

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Studies of less than 4 weeks' duration were excluded since this short time frame may be insufficient to appropriately evaluate the effects of antipsychotic agents. Studies focusing specifically on the elderly population (≥ 65 years) or on inpatients were excluded because they are not applicable to the patient population under consideration. Studies that did not use the standard rating scales described below were also excluded. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Clinical trials included focus on outpatient treatment; thus, while immediate-release injectables have demonstrated efficacy in placebo-controlled and/or comparative trials, details are not included in this review.

Approval of aripiprazole tablets with sensor (Abilify Mycite) is based on data with standard aripiprazole tablets (Abilify).[443]

Bipolar Disorder

Efficacy Scales

CGI-BP (Clinical Global Impression – bipolar) – The CGI was modified specifically for use in assessing global illness severity and change in patients with bipolar disorder.[444]

HAM-D (Hamilton Depression Rating Scale) – This scale is used to assess the severity of major depressive disorder (MDD) in patients already diagnosed with an affective disorder. It is the most widely used and accepted outcome measure for evaluating depression severity. The HAM-D is the standard depression outcome measure used in clinical trials presented to the FDA by pharmaceutical companies for approval of New Drug Applications. The standard HAM-D-21 contains 21 questions. The more commonly used HAM-D-17 excludes 4 questions relating to diurnal variation, de-personalization and de-realization, paranoid symptoms, and obsessional and compulsive symptoms. The remaining 17

questions are related to symptoms, such as depressed mood, guilty feelings, suicide, sleep disturbances, anxiety levels, and weight loss.[445]

MADRS (Montgomery-Asberg Depression Rating Scale) – This scale measures the effect of treatment on depression severity and, as such, requires a baseline assessment before treatment with subsequent assessments during the course of treatment. The MADRS measures the severity of a number of symptoms, including mood and sadness, tension, sleep, appetite, energy, concentration, suicidal ideation, and restlessness.[446]

YMRS (Young Mania Rating Scale) – This scale is used to assess disease severity in patients already diagnosed with mania. It is a checklist of 11 manic symptoms that is administered by a trained clinician based on a personal interview.[447] The scale, which follows the style of the HAM-D, was designed to be sensitive to the effects of treatments on manic symptoms.

Bipolar Disorder - Mania

aripiprazole (Abilify) versus haloperidol

In a double-blind study, investigators randomized 347 patients with bipolar I disorder experiencing acute manic or mixed episodes to receive either oral aripiprazole 15 mg/day or haloperidol 10 mg/day for 12 weeks.[448] Doses could be increased after week 1 or 2 to aripiprazole 30 mg or haloperidol 15 mg. Average daily dosages at week 12 were aripiprazole 21.6 mg and haloperidol 11.1 mg, respectively. At the conclusion of the study, response (defined as at least a 50% improvement in YMRS) was noted in 50% of patients randomized to aripiprazole and 28% of patients receiving haloperidol ($p<0.001$). These rates were similar to the continuation rates of 51 and 29%, respectively. The study was funded by the manufacturer of aripiprazole.

aripiprazole (Abilify) versus placebo in pediatrics

Patients (n=296) ages 10 to 17 years with bipolar I disorder with current manic or mixed episodes, with or without psychotic features, and a Young Mania Rating Scale (YMRS) score ≥ 20 were enrolled in a randomized, multicenter, double-blind 4-week study.[449,450] The primary endpoint was change from baseline in the YMRS total score. Both doses of aripiprazole were superior to placebo in the change in YMRS total score at week 4.

asenapine (Saphris) versus placebo

The efficacy of asenapine for the treatment of acute manic or mixed episodes associated with bipolar I disorder as monotherapy was established in two, 3-week, randomized, double-blind, placebo-controlled or active-controlled (olanzapine) trials in adults (n=283 and n=488).[451,452,453,454] In both trials, patients were randomized to 10 mg of asenapine twice daily (5 mg twice daily allowed), placebo, or active comparator, and asenapine was superior to placebo after 3 weeks in the YMRS total score and CGI-BP severity of illness (mania) score). YMRS response and remission rates with olanzapine, but not asenapine, exceeded those of placebo. A third 3-week trial comparing asenapine 5 or 10 mg twice daily to placebo had similar findings.

The efficacy of asenapine for the treatment of acute manic or mixed episodes associated with bipolar I disorder as adjunctive therapy was established in a 12-week, randomized, double-blind, placebo-controlled trial in adults.[455] Patients were randomized to asenapine 5 to 10 mg twice daily or placebo.

After 3 weeks, asenapine was superior to placebo in reducing manic symptoms as measured by the YMRS total score, the primary outcome.

asenapine (Saphris) versus placebo in pediatrics

The efficacy of asenapine for acute mania associated with bipolar disorder in patients ages 10 to 17 years was established in a single, 3-week, placebo-controlled, double-blind trial (n=403) comparing asenapine 2.5, 5, or 10 mg twice daily to placebo.[456] At Week 3, asenapine significantly improved YMRS total score and CGI-BP severity of illness score.

loxapine inhalation powder (Adasuve) versus placebo

The efficacy of loxapine inhalation powder in the acute treatment of agitation associated with bipolar I disorder (n=314) was established in a short-term (24-hour) randomized, double-blind, placebo-controlled, fixed-dose trial.[457] Inhaled loxapine significantly reduced agitation compared with placebo as assessed by change from baseline in the PEC score 2 hours after dosing (primary endpoint) and Clinical Global Impression scale – Improvement (CGI-I) score at 2 hours. This was apparent 10 minutes following dosing.

olanzapine (Zyprexa) versus haloperidol

In a double-blind study, 453 patients with bipolar mania were randomized to receive oral olanzapine 5-20 mg/day or haloperidol 3 to 15 mg/day for 2 successive 6-week periods.[458] Remission rates at week 6, as determined by YMRS ≤ 12 and HAM-D ≤ 8, were similar in the olanzapine and haloperidol groups (52% and 46%, respectively; p=0.15). Relapse rates were also similar (13% to 15%) in each group. Worsening of EPS was more common with haloperidol. Weight gain was noted only with olanzapine (2.8 kg; p<0.001 compared to haloperidol). The study was performed by the manufacturer of olanzapine.

olanzapine (Zyprexa) versus placebo in pediatrics

The safety and efficacy of oral olanzapine were evaluated in a 3-week, double-blind, flexible-dose, placebo-controlled, randomized acute treatment trial of adolescents (ages 13 to 17 years) with manic or mixed episodes associated with bipolar I disorder (n=161).[459] Olanzapine resulted in a statistically significantly greater mean reduction in YMRS total score compared to placebo.

quetiapine (Seroquel) versus haloperidol and placebo

Investigators randomized 302 patients with bipolar mania to receive double-blind treatment with quetiapine up to 800 mg/day, haloperidol up to 8 mg/day, or placebo for 12 weeks.[460] While both active treatments were superior to placebo in improvement in YMRS at day 21, haloperidol also was superior to quetiapine (p<0.05). There was no significant difference between active treatments at any other weekly assessment during the study. Both active treatments maintained their superiority over placebo throughout the study. Response rates at day 84 were higher with quetiapine (61%) and haloperidol (70%) than with placebo (39%; p<0.05); there was no significant difference between active treatments. Withdrawal rates were approximately 54% for each of the active treatments and 42% for placebo (p<0.05). Withdrawal due to adverse events was twice as common with haloperidol as with quetiapine or placebo.

quetiapine ER (Seroquel XR) versus placebo

The efficacy of quetiapine ER for the acute treatment of manic or mixed episodes was established in a 3-week, randomized, placebo-controlled trial in adults with bipolar I disorder (n=316).[461] Patients were randomized to quetiapine ER 400 to 800 mg/day or placebo. After 3 weeks, quetiapine ER was superior to placebo in reduction of YMRS total score. Data with quetiapine (Seroquel) in 3 placebo-controlled trials in patients with mania associated with bipolar I disorder (as either monotherapy or adjunct therapy) were also extrapolated to establish efficacy of quetiapine ER in this population.

quetiapine (Seroquel) versus placebo in pediatrics

The efficacy of quetiapine for the acute treatment of manic episodes associated with bipolar I disorder (based on DSM-IV criteria) in patients ages 10 to 17 years was established in a 3-week, double-blind, placebo-controlled, multicenter trial (n=284).[462,463] Patients were randomized to quetiapine 400 or 600 mg/day (in divided doses) or to placebo. After 3 weeks, both quetiapine doses demonstrated superiority over placebo in change in reduction in YMRS total score.

Efficacy of quetiapine ER (Seroquel XR) in this population was extrapolated from data with immediate-release quetiapine (Seroquel).[464]

risperidone (Risperdal) versus haloperidol and placebo

In a double-blind study, 438 patients were randomized to receive risperidone 1-6 mg/day (mean dose 4.2 mg/day), haloperidol 2 to 12 mg/day (8 mg/day), or placebo for 3 weeks, followed by 1 of the active treatments for an additional 9 weeks for the management of bipolar mania.[465] At week 3 and throughout the remaining 9 weeks, mean YMRS reductions from baseline were greater in patients receiving either active treatment than those receiving placebo. There was no significant difference between risperidone and haloperidol. EPS occurred more often in the haloperidol group than in the risperidone or placebo groups.

risperidone (Risperdal) versus placebo in pediatrics

The safety and efficacy of risperidone for the treatment of manic or mixed episodes in children or adolescents (ages 10 to 17 years) with bipolar I disorder was evaluated in a double-blind, randomized, placebo-controlled trial (n=169).[466,467] Patients were randomized to risperidone 0.5 mg/day to 2.5 mg/day, risperidone 3 mg/day to 6 mg/day, and placebo. There was significant improvement in the mean YMRS total score, the primary outcome, in both risperidone groups when compared to placebo at the end of 3 weeks ($p<0.001$ for both).

ziprasidone (Geodon) versus placebo

Efficacy of ziprasidone (Geodon) as monotherapy for the treatment of acute mixed or manic episodes associated with bipolar I disorder (based on DSM-IV criteria) was established in two, 3-week, double-blind, placebo-controlled, randomized clinical trials.[468] In both Study 1 (n=210) and Study 2 (n=205) patients were randomized to ziprasidone 40 to 80 mg twice daily (mean dose 112 to 132 mg/day) or placebo. In both trials, ziprasidone demonstrated superiority over placebo in reduction in Mania Rating Scale (MRS) total score and Clinical Global Impression scale – Severity (CGI-S).

Bipolar Disorder – Depression

lurasidone (Latuda) versus placebo

The efficacy of lurasidone, as monotherapy, was established in a 6-week, double-blind, placebo-controlled, multicenter, study of adults who met DSM-IV-TR criteria for major depressive episodes associated with bipolar I disorder (n=503).[469] Patients were randomized to receive lurasidone (20 to 60 mg/day or 80 to 120 mg/day) or placebo for 6 weeks. Lurasidone treatment significantly reduced mean MADRS total scores for both the 20 to 60 mg/day group and the 80 to 120 mg/day compared to placebo, the primary outcome. Greater endpoint reduction in CGI-BP depression severity scores were also achieved in both groups compared to placebo.

The efficacy of lurasidone as adjunctive therapy with lithium or valproate for the treatment of major depressive episodes associated with bipolar I disorder, was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of adult patients (n=340).[470] Patients were randomized to flexibly dose lurasidone (20 to 120 mg/day) or placebo. After 6 weeks, lurasidone was superior to placebo in change in baseline MADRS score, the primary endpoint, and CGI-BP severity score.

lurasidone (Latuda) versus placebo in pediatrics

A 6-week, multicenter, randomized, double-blind, placebo-controlled study established the efficacy of lurasidone in pediatric patients (10 to 17 years) with a major depressive episode associated with bipolar I disorder (with or without rapid cycling and without psychotic features) (n=347).[471,472] Patients were randomized to oral lurasidone (flexible dosing of 20 mg to 80 mg per day) or placebo. The primary endpoint was the change from baseline in the Children's Depression Rating Scale, Revised (CDRS-R) total score (17-item clinician-rated scale; score range, 17 to 113) at week 6. Lurasidone was superior to placebo in this endpoint (-21 versus -15.3, respectively; $p<0.0001$).

olanzapine/fluoxetine (Symbyax) versus olanzapine (Zyprexa) and placebo

An 8-week clinical trial in 833 adults with depression associated with bipolar I disorder found the olanzapine/fluoxetine combination (doses of 6/25 mg, 6/50 mg, or 12/50 mg per day) was more effective than oral olanzapine alone (5 to 20 mg/day) or placebo.[473] At week 8, MADRS remission criteria were met by 25% of the placebo group, 33% of the olanzapine group, and 49% of olanzapine/fluoxetine group. Treatment-emergent mania did not differ among groups (placebo 6.7%, olanzapine 5.7%, and olanzapine/fluoxetine 6.4%). Adverse events for olanzapine/fluoxetine therapy were similar to those for olanzapine therapy but also included higher rates of nausea and diarrhea. A secondary analysis was completed to determine the benefits of olanzapine alone and olanzapine/fluoxetine for improving HRQOL using both a generic and a depression-specific HRQOL instrument.[474] Based on the analyses, patients with bipolar depression receiving olanzapine or olanzapine/fluoxetine for 8 weeks had greater improvement in HRQOL than those receiving placebo. Treatment with olanzapine/fluoxetine was associated with greater improvement in HRQOL than olanzapine alone. Olanzapine monotherapy is not approved for the treatment of depressive episodes associated with bipolar disorder.

olanzapine/fluoxetine (Symbyax) versus placebo in pediatrics

The efficacy of olanzapine/fluoxetine for the treatment of depressive episodes associated with bipolar disorder was established in one, 8-week, randomized, double-blind, placebo-controlled trial in patients

10 to 17 years old who met DSM-IV-TR criteria for bipolar I disorder, currently depressed.[475] Patients were randomized to flexibly dosed olanzapine/fluoxetine (mean dose, 7.7/37.6 mg) or placebo. After 8 weeks, the change in baseline CDRS-R with olanzapine/fluoxetine was significantly superior to placebo. The CDRS-R is a 17-item clinician-rated sale with scores ranging from 17 to 113.

quetiapine (Seroquel) versus placebo

The efficacy of quetiapine for the acute treatment of depressive episodes associated with bipolar disorder was established in two, 8-week, double-blind, placebo-controlled, randomized trials in adults with bipolar I or II disorder (n=1,045).[476] In both trials, patients were randomized to quetiapine (300 or 600 mg) or placebo once daily. In both trials, quetiapine was superior to placebo in reduction in MADRS score at Week 8, the primary endpoint. No additional benefit was seen with the 600 mg dose over the 300 mg dose.

quetiapine ER (Seroquel XR) versus placebo

The efficacy of quetiapine ER for the acute treatment of depressive episodes associated with bipolar disorder was established in an 8-week, double-blind, placebo-controlled, randomized trial in adults with bipolar I or II disorder (n=280).[477,478] Patients were randomized to either quetiapine ER 300 mg once daily or placebo. Quetiapine ER was superior to placebo in reduction in MADRS score at Week 8, the primary endpoint. Remission rates at week 8 based on MADRS scores were significantly higher with quetiapine ER compared with placebo.

Bipolar Disorder – Maintenance

aripiprazole (Abilify) versus placebo

The efficacy of aripiprazole maintenance treatment for bipolar I disorder (based on DSM-IV criteria) as monotherapy was established in a placebo-controlled, treatment withdrawal trial (n=161).[479] Patients stabilized on open-label aripiprazole (15 or 30 mg/day) were randomized to continue adjunct aripiprazole therapy or placebo in a double-blind phase. Aripiprazole was superior to placebo in time to relapse (manic or depressive episode), the primary endpoint, over approximately 180 days following randomization.

The efficacy of aripiprazole maintenance treatment for bipolar I disorder (based on DSM-IV criteria) as adjunctive therapy to lithium or valproate was established in a placebo-controlled, treatment withdrawal trial (n=161).[480] Patients stabilized on open-label aripiprazole (10 to 30 mg/day) were randomized to continue aripiprazole therapy or placebo in a double-blind phase. Aripiprazole was superior to placebo in time to relapse (manic, mixed, or depressive episode), the primary endpoint, over 52 weeks following randomization. The number of manic episodes with aripiprazole was fewer than with placebo; however, the number of depressive episodes with aripiprazole did not differ statistically from placebo.

asenapine (Saphris) versus placebo

The use of asenapine for maintenance monotherapy for bipolar I disorder was evaluated in a placebo-controlled, double-blind, multicenter, flexible dose (5 mg or 10 mg twice depending on tolerability) clinical trial.[481,482] Patients were initiated and stabilized on asenapine in a 12 to 16 week open-label phase (n=549) and were subsequently randomized to either continue treatment or switch to placebo in

a treatment-withdrawal, double-blind phase (n=252). The study demonstrated that asenapine was statistically superior to placebo in time to relapse.

olanzapine (Zyprexa) versus placebo

The efficacy of olanzapine maintenance treatment for bipolar I disorder (based on DSM-IV criteria) as monotherapy was established in a placebo-controlled, treatment withdrawal trial (n=361).[483] Following a stabilization phase on olanzapine 5 to 20 mg/day, patients were randomized to continue the same dose or to placebo. During the randomized, double-blind phase, patients on olanzapine had a greater time to relapse compared to placebo.

quetiapine (Seroquel) versus placebo

The efficacy of quetiapine as an adjunctive maintenance treatment for bipolar I disorder with lithium or divalproex (based on DSM-IV criteria) was established in 2 placebo-controlled trials (n=1,326).[484] Patients stabilized on quetiapine during an open-label phase were randomized to adjunct quetiapine (400 to 800 mg/day) or placebo in a treatment withdrawal design. The primary endpoint was time to recurrence of a mood event (manic, mixed, or depressed episode). In both studies, quetiapine was superior to placebo in increasing time to mood episode recurrence.

Data from quetiapine (Seroquel) were extrapolated for FDA approval of quetiapine ER (Seroquel XR) in this population.[485]

ziprasidone (Geodon) versus placebo

The efficacy of ziprasidone as an adjunctive maintenance treatment for bipolar I disorder with lithium or valproate (based on DSM-IV criteria) was established in a placebo-controlled treatment withdrawal trial (n=239).[486,487] Patients were stabilized on adjunctive ziprasidone (80 to 160 mg divided twice daily) during an open-label phase. Patients were then randomized to continue ziprasidone or to placebo. Ziprasidone was superior to placebo in time to recurrence of a mood episode (manic, mixed, or depressed) requiring intervention, the primary endpoint.

Irritability Associated with Autistic Disorder

Efficacy Scales

ABC (Aberrant Behavior Checklist) – This scale is a 58-item third-party informant rating scale originally developed to monitor an array of behavioral features among patients with mental retardation. It relies on clinical observations of activity and behavior and has been validated in children with concomitant autistic and psychotic disorders.[488,489]

CARS (Childhood Autism Rating Scale) – This is the most widely used standardized instrument specifically designed to aid in the diagnosis of autism in children as young as 2 years of age. This scale includes items from 5 prominent systems for diagnosing autism. Each item covers a particular characteristic, ability, or behavior. This test combines parent reports and direct observation by a professional.[490]

NCBRF (Nisonger Child Behavior Rating Form) – This is a standardized instrument for assessing child and adolescent behavior. There are 2 levels of this form; 1 of these is for children with developmental disabilities, specifically mental retardation and/or autism spectrum disorders. There is 1 version of the form for completion by parents and 1 for completion by teachers.[491]

aripiprazole (Abilify) versus placebo

Efficacy of aripiprazole in the treatment of irritability associated with autistic disorder was established in two, 8-week clinical trials in patients ages 6 to 17 years old who met the DSM-IV criteria for autistic disorder.[492] In Study 1 (n=98), patients received doses of aripiprazole (2 mg to 15 mg/day) or placebo. Efficacy was measured using the ABC-irritability (ABC-I) scale and the CGI-I. At the end of the 8-week trial, improvements were significant in the ABC-I and CGI-I scales, with the mean daily dose of aripiprazole of 8.6 mg/day. In Study 2, 218 children and adolescents were treated with 3 fixed doses of aripiprazole (5 mg/day, 10 mg/day or 15 mg/day) compared to placebo.[493] At the end of the 8-week trial, all 3 doses of aripiprazole showed significantly improved scored on the ABC-I subscale compared to placebo.

risperidone (Risperdal) versus placebo

The efficacy of risperidone in the treatment of irritability associated with autistic disorder was established in two, 8-week, placebo-controlled trials in children and adolescents (aged 5 to 16 years) who met the DSM-IV criteria for autistic disorder.[494,495] In Study 1 (n=101), patients received twice daily doses of placebo or risperidone, starting at 0.25 mg/day or 0.5 mg/day depending on baseline weight (< 20 kg and ≥ 20 kg, respectively) and titrated to clinical response (mean modal dose of 1.9 mg/day, equivalent to 0.06 mg/kg/day). Risperidone significantly improved scores on the ABC-I and on the Clinical Global Impression scale –Change (CGI-C) compared with placebo. In Study 2 (n=55), patients received placebo or risperidone 0.02 to 0.06 mg/kg/day given once or twice daily, starting at 0.01 mg/kg/day and titrated to clinical response (mean modal dose of 0.05 mg/kg/day, equivalent to 1.4 mg/day). Risperidone significantly improved scores on the ABC-I subscale compared with placebo.

A third trial of 6 weeks in duration, which was also used to establish efficacy, randomized pediatric patients 5 to 17 years of age with autistic disorder to low-dose (0.125 to 0.175 mg; weight-based) or high-dose (1.25 to 1.75 mg; weight-based) risperidone once daily or placebo. High-dose risperidone demonstrated superiority over placebo in ABC-I at 6 weeks, but low-dose risperidone did not.[496]

Major Depressive Disorder

Efficacy Scales

CGI-I (Clinical Global Impression – Global Improvement) – This 3-item scale assesses the patient's improvement or worsening by comparing a patient's baseline condition with his or her current condition.[497]

MADRS (Montgomery Asberg Depression Rating Scale) – This scale measures the effect of treatment on depression severity and, as such, requires a baseline assessment before treatment with subsequent assessments during the course of treatment. The MADRS measures the severity of a number of symptoms, including mood and sadness, tension, sleep, appetite, energy, concentration, suicidal ideation, and restlessness.[498]

QIDS-SR (Depressive Symptomatology-Self-Report) – This self-assessment scale was developed from the 30-item Inventory of Depressive Symptomatology (IDS).[499] All criteria are based on the DSM-IV criterion for major depressive disorder. This assessment has been validated to have similar sensitivity to both the HAM-D and the IDS-SR.

aripiprazole (Abilify) versus placebo

The efficacy of aripiprazole in the adjunctive treatment of major depressive disorder was evaluated in two, 6-week, placebo controlled trials in adults with prior inadequate response to 1 to 3 courses of antidepressants for the current episode.[500,501,502] Antidepressant therapy comprised of 1 of the following: escitalopram, fluoxetine, paroxetine CR, sertraline, or venlafaxine ER. In both trials, patients were randomized to aripiprazole 5 to 20 mg/day (mean doses of 10.7 and 11.4 mg/day in the 2 trials) or placebo in addition to background antidepressant therapy. In Study 1 (n=381) and Study 2 (n=362), aripiprazole was superior to placebo in reducing the mean MADRS score, the primary endpoint. In 1 trial, aripiprazole also was superior to placebo in mean Sheehan Disability Scale (SDS), a self-rated instrument used to assess the impact of depression.

brexpiprazole (Rexulti) versus placebo

Two 6-week, double-blind, placebo-controlled, fixed-dose trials in adult patients were performed to evaluate the efficacy of brexpiprazole in the adjunctive treatment of MDD (DSM-IV criteria).[503,504] Study participants were required to have an inadequate response to prior antidepressant therapy (1 to 3 courses) in the current episode and show an inadequate response (symptoms persisted without substantial improvement) throughout the 8 weeks of prospective antidepressant treatment (escitalopram, fluoxetine, paroxetine controlled-release, sertraline, duloxetine delayed-release, or venlafaxine extended-release). Patients in Study 1 were randomized to brexpiprazole 2 mg once daily or placebo. Patients in Study 2 were randomized to brexpiprazole 1 mg or 3 mg once daily or placebo. In both studies, brexpiprazole was superior to placebo in difference in mean MADRS total scores, the primary endpoint.

olanzapine/fluoxetine combination (Symbyax) versus olanzapine (Zyprexa) and fluoxetine

Two parallel, 8-week, double-blind studies compared olanzapine/fluoxetine combination, oral olanzapine, and fluoxetine in outpatients with treatment-resistant depression, defined as a documented history of current-episode antidepressant failure plus a prospective failure of fluoxetine.[505] Following an 8-week fluoxetine lead-in, 605 non-responders with DSM-IV MDD were randomly assigned to olanzapine/fluoxetine combination, olanzapine, or fluoxetine. The primary outcome measure was baseline-to-endpoint mean change on the MADRS. Patients having failed treatment with 2 antidepressants taking olanzapine/fluoxetine combination exhibited greater improvement in depressive symptoms than patients taking olanzapine or fluoxetine in 1 of 2 studies and in the pooled analysis.

quetiapine ER (Seroquel XR) versus placebo

Data were analyzed from two, 6-week, multicenter, double-blind, randomized, placebo-controlled studies, prospectively designed to be pooled. Patients received once-daily quetiapine ER 150 mg daily (n=309), 300 mg daily (n=307), or placebo (n=303) adjunctive to ongoing antidepressant therapy.[506,507] Quetiapine ER (150 mg and 300 mg daily) reduced MADRS total scores compared to placebo at every assessment including week 6 and week 1. Quetiapine ER 150 mg and 300 mg daily significantly improved MADRS response and remission and HAM-D, HAM-A, PSQI, and CGI-S scores at week 6 compared to placebo.

Psychotic Disorders, including Schizophrenia

Efficacy Scales

The 2 scales most commonly used for measuring symptom reduction of schizophrenia patients in clinical trials are the BPRS and PANSS.

BPRS (Brief Psychiatric Rating Scale) – This is a 16-item scale with 9 general symptom items, 5 positive-symptom items, and 2 negative-symptom items. It is completed by the physician with each item scored on a 7-point severity scale.[508]

PANSS (Positive and Negative Syndrome Scale) – This is a 30-item scale with 16 general psychopathology symptom items, 7 positive-symptom items, and 7 negative symptom items. The physician completes this scale by scoring each item on a 7-point severity scale. The positive- and negative-symptom item groups are often reported separately.[509]

Other scales are also used, depending on the specific outcomes being studied.

CGI-S (Clinical Global Impression – Severity) – This 3-item scale assesses the clinician's impression of the current state of the patient's illness and provides an assessment of the patient's current symptom severity. The rater is asked to consider his total clinical experience with the given population.[510]

HRQOL (Health Related Quality Of Life) – HRQOL includes measurements of physical and social function, psychological status, functional capacity, somatic sensation, and the sense of well-being impacted by health status.

MLDL (Munich Life Quality Dimension List) – This scale measures subjective quality of life (QoL) by having subjects respond in terms of both satisfaction and importance on a 0-10 scale. This is an instrument for cognitive assessment of elementary components (physical condition, psyche, social life, everyday life) of quality of life.

NSA-16 (Negative Symptom Assessment) – The NSA-16 was developed to evaluate the presence and severity of negative symptoms of schizophrenia. This assessment is a multidimensional structure consisting of 5 factors: communication, emotion/affect, social involvement, motivation, and retardation.[511]

PEC (Positive and Negative Syndrome Scale-Excited Component) – This is an investigator-rated instrument consisting of 5 items: poor impulse control, tension, hostility, uncooperativeness, and excitement. Each item is scored on a scale from 1 (absent) to 7 (extreme). The total PEC score can range from 5 to 35.

PHQ-9 (9-item Patient Health Questionnaire) – This is a self-administered version of PRIME-MD instrument commonly used for mental disorders.[512] Depression symptoms are self reported and range from 0 (not at all) to 3 (nearly every day). The questions incorporate diagnostic criteria associated with depression as identified in the DSM-IV.

SANS (Scale for the Assessment of Negative Symptoms) – This scale assesses 5 symptom complexes to obtain clinical ratings of negative symptoms in patients with schizophrenia. These symptom complexes are affective blunting, alogia (impoverished thinking), avolition/apathy, anhedonia, and disturbance of attention.[513]

SAPS (Scale for the Assessment of Positive Symptoms) – This scale is designed to assess positive symptoms, primarily those that occur in schizophrenia.[514]

SWN (Subjective Well-Being under Neuroleptic Treatment Scale) – This subjective scale is mainly influenced by psychopathological status in patients receiving second generation antipsychotics (SGAs). SWN has been shown to significantly correlate with the PANSS.[515]

VAS (Visual Analog Scale) – The VAS is one of the most frequently used measurement scales in health care research, most commonly used for the measurement of pain. This scale measures the intensity or magnitude of sensations and subjective feelings and the relative strength of attitudes and opinions about specific stimuli.[516,517,518]

First Generation Antipsychotics (FGAs)

SGAs were developed in response to problems with FGAs, including lack of efficacy in some patients, lack of improvement in negative symptoms, and troublesome adverse effects, especially EPS and TD.[519] Multiple studies have been performed between the first- and second-generation agents, but the results are not clear when considering the aggregate of available information. Although the SGAs are commonly thought to have superior effectiveness against the negative symptoms of psychotic disorders, most studies have not sought to prove that point. Clozapine (Clozaril) and oral ziprasidone (Geodon) do have data that show increased effectiveness in negative symptoms compared to chlorpromazine and haloperidol.[520,521,522] Results from trials that evaluated oral olanzapine (Zyprexa) and risperidone (Risperdal) do not give results consistent with this claim.[523,524,525,526] In general, there is inconclusive evidence that the overall effectiveness of SGAs is better than that for FGAs in terms of meeting primary outcomes of changes in rating scale scores. However, it is well documented that SGAs are associated with less EPS than FGAs.[527,528,529,530,531,532,533,534,535,536,537,538] While that is a distinct advantage, there is the question of long-term adverse events (such as metabolic disorders) linked to SGA use. There is also the question of long-term effectiveness with antipsychotics. Many studies are under 12 weeks in duration, which is not the optimal study timeframe for measuring therapies for a lifelong illness. Likewise, a study of clozapine and chlorpromazine over 12 months showed no difference in effectiveness.[539] Risperidone showed continued effectiveness over 3 and 12 months in 2 different studies using haloperidol as a comparator.[540,541] For olanzapine, 2 studies with haloperidol at least 1 year in duration showed mixed results.[542,543] The follow-up rates for studies in patients with these mental health disorders are usually poor. This is easily illustrated by the CATIE study, which had a follow-up rate of 26% over the course of 18 months in Phase 1.[544] All of these issues cloud the issue of the presence of a detectable clinical difference between FGAs and SGAs in efficacy and overall adverse effect profiles.

loxapine inhalation powder (Adasuve) versus placebo

The efficacy of loxapine inhalation powder in the acute treatment of agitation associated with schizophrenia (n=344) was established in a short-term (24-hour) randomized, double-blind, placebo-controlled, fixed-dose trial.[545] Inhaled loxapine significantly reduced agitation compared with placebo in change from baseline in the PEC score 2 hours after dosing (primary endpoint) and CGI-I score at 2 hours. This was apparent 10 minutes following dosing.

aripiprazole (Abilify) versus risperidone (Risperdal) and placebo

In a 4-week, double-blind study, 404 patients with schizophrenia or schizoaffective disorder were randomized to oral aripiprazole 20 mg daily, aripiprazole 30 mg daily, risperidone 6 mg daily, or placebo.[546] Efficacy assessments included the PANSS and CGI score. Safety and tolerability evaluations included the incidence of EPS, effects on weight, prolactin levels, and QT interval. Aripiprazole and risperidone were better than placebo on all efficacy measures. Separation from placebo occurred at week 1 for PANSS total and positive scores with aripiprazole and risperidone, and for PANSS negative scores with aripiprazole. There were no significant differences between aripiprazole and placebo in mean change from baseline in the EPS rating scales. Mean prolactin levels decreased with aripiprazole but increased 5-fold with risperidone. Mean change in QT interval did not differ significantly from placebo with any active treatment group. Aripiprazole and risperidone groups showed a similarly low incidence of clinically significant weight gain. Aripiprazole is not indicated for schizoaffective disorder.

aripiprazole (Abilify) versus placebo in pediatrics

The efficacy of aripiprazole in the treatment of pediatric schizophrenia was established in a 6-week, randomized, double-blind, multicenter, placebo-controlled study of patients ages 13 to 17 years of age (n=302) who met DSM-IV criteria for schizophrenia and had a Positive and Negative Syndrome Scale (PANSS) greater than or equal to 70 at baseline.[547,548] Patients were randomized to receive oral aripiprazole 10 mg/day, aripiprazole 30 mg/day, or placebo. The primary outcome measure of the study indicated that oral aripiprazole (10 mg/day and 30 mg/day) leads to better symptom control of schizophrenia over placebo based on a greater reduction in the PANSS total score. Study results also demonstrated an improvement over placebo in PANSS positive subscale, PANSS negative subscale, CGI-S, and CGI-I. The study did not demonstrate a significant difference in efficacy between the 10 mg/day dose and the 30 mg/day dose of aripiprazole.

A multicenter, double-blind, placebo-controlled, randomized withdrawal design trial assessed the longer-term efficacy of aripiprazole in patients ages 13 to 17 years with schizophrenia (as defined by the DSM-IV-TR).[549] Patients were first transitioned from oral medication to oral aripiprazole (weeks 0 to 6) and stabilized on a dose of 10 mg to 30 mg per day (weeks 7 to 21). They were then randomized 2:1 to continue aripiprazole or to placebo for up to 52 weeks (n=146). The primary endpoint was the time to exacerbation of psychotic symptoms or impending relapse, which was found to be longer in those continuing aripiprazole compared to those who were switched to placebo (hazard ratio [HR], 0.46; 95% CI, 0.24 to 0.88; p=0.016).

asenapine (Saphris) versus olanzapine (Zyprexa)

Two randomized, double-blind, 26-week core studies were conducted in Eastern (EH) and Western Hemisphere (WH) countries and tested the hypothesis that asenapine is superior to olanzapine for persistent negative symptoms of schizophrenia; 26-week extension studies assessed the comparative long term efficacy and safety of these agents.[550] In the core studies, 949 people were randomized to asenapine (n=241 and 244 in Studies 1 and 2, respectively) or olanzapine (n=240 and 224 in Studies 1 and 2, respectively) while there were 134 and 86 asenapine participants and 172 and 110 olanzapine participants in the EH and WH extensions, respectively. The 16-item NSA-16 total score was the primary efficacy variable used to assess negative symptoms. Asenapine was not superior to olanzapine in change in the NSA-16 total score in either core study (EH: p=0.79; WH: p=0.72). Asenapine was superior to olanzapine at week 52 in the WH extension study; however, these positive results need to

be interpreted in view of the fact that only a relatively small subset of participants continued in the extension study. Incidence of treatment-emergent adverse events was comparable between treatments across studies. Weight gain was consistently lower with asenapine. Extrapyramidal symptoms were higher with asenapine compared to olanzapine but abbreviated total score changes did not significantly differ between treatments. In conclusion, asenapine superiority over olanzapine for treatment of persistent negative symptoms was not observed in these studies. Both treatments improved persistent negative symptoms, but discontinuation rates were higher with asenapine. This study was funded both by Merck, the manufacturer of asenapine, and Pfizer.

brexpiprazole (Rexulti) versus placebo

Two, 6-week, randomized, double-blind, placebo-controlled, fixed-dose trials were performed in adult patients to assess the efficacy of brexpiprazole (2 or 4 mg) in the treatment of schizophrenia.[551,552] Patients were required to meet the DSM-IV-TR criteria for schizophrenia. In Study 1, both the 2 mg daily and 4 mg daily were superior to placebo on the PANSS total score, the primary endpoint. In Study 2, only the 4 mg per day dose was superior to placebo in the PANSS total score.

In a third double-blind study using a treatment withdrawal design, adult patients with schizophrenia were randomized to either continue brexpiprazole at a stable dose (n=97) or placebo (n=105) following a 12-week stabilization period (dose range, 1 to 4 mg/day).[553] A prespecified interim analysis using Kaplan-Meier curves of relapse using multiple definitions, including change in CGI-I and PANSS, hospitalization, and suicidal or violent/aggressive behavior, found a significantly longer time to relapse in patients randomized to continue brexpiprazole compared to those randomized to switch to placebo.

cariprazine (Vraylar) versus placebo

The safety and efficacy of cariprazine were established in three 6-week, double-blind, randomized, placebo-controlled trials in patients diagnosed with schizophrenia.[554,555,556,557] In all 3 trials, patients ages 18 to 60 years were required to meet diagnostic criteria for schizophrenia based on the DSM-IV-TR. In all 3 trials, the change in PANSS score from baseline was the primary outcome while the change in CGI-S was a secondary efficacy measure. Study 1 (n=711) compared 3 fixed doses of cariprazine (1.5, 3, and 4.5 mg) to placebo, Study 2 (n=604) compared 2 fixed doses of cariprazine (3 and 6 mg) to placebo, and Study 3 (n=439) compared 2 flexible dose ranges of cariprazine (3 to 6 and 6 to 9 mg/day) and an active-control (aripiprazole) to placebo. All 3 trials demonstrated superiority of cariprazine over placebo at 6 weeks in PANSS and CGI-S.

A multinational, randomized, double-blind, placebo-controlled, parallel-group study evaluated the longer-term efficacy and safety of cariprazine in adults with schizophrenia.[558,559] Patients with schizophrenia symptoms were treated with cariprazine 3 mg to 9 mg daily during the 20-week open-label phase. Stabilized patients were then randomized to continued cariprazine or placebo in a double-blind treatment phase for up to 72 weeks (n=200). The primary endpoint was the time to relapse, defined as worsened symptom scores on the PANSS or CGI-S, select notable/severe symptom scores on the PANSS, psychiatric hospitalization, aggressive or violent behavior, or suicidal risk, using Kaplan-Meier curves. Relapse occurred in 24.8% of patients treated with cariprazine compared to 47.5% of placebo-treated patients (HR, 0.45; 95 CI, 0.28 to 0.73; the risk for relapse was lower with continued cariprazine compared to placebo; p=0.001). Per the product labeling, doses exceeding 6 mg/day are not recommended due to an increase in adverse effects.

clozapine versus olanzapine (Zyprexa)

A randomized, double-blind, parallel study compared treatment with either clozapine (100 to 500 mg/day) or oral olanzapine (5 to 25 mg/day) in 147 patients with schizophrenia, who were either nonresponsive or intolerant of standard antipsychotic therapy.[560] At the 18-week endpoint, no statistically significant differences were found among olanzapine and clozapine based on the efficacy measures used, PANSS and CGI-S. Response rates were not significantly different between olanzapine-treated patients (58%) and clozapine-treated patients (61%). There were no significant differences in either group in regards to occurrences of EPS, and no clinically or statistically significant changes observed in vital signs, electrocardiograms, or laboratory measures. Both treatments were well tolerated.

In another study, 114 patients with schizophrenia were randomized to clozapine (100 to 400 mg/day) or oral olanzapine (5 to 25 mg/day) for 26 weeks.[561] The double-blind, multicenter trial evaluated the effects of each drug on subjective (SWN, MLDL) and clinical (PANSS and CGI-S) outcomes. The SWN scores improved significantly in both groups. Olanzapine (mean dose 16.2 mg/day) was not inferior to clozapine (mean dose 209 mg/day; group difference 3.2 points in favor of olanzapine; 95% CI, 4.2 to 10.5). MLDL, PANSS, and CGI-S scores improved similarly in each group.

iloperidone (Fanapt) and placebo

The efficacy and safety of iloperidone in patients with acute exacerbations of schizophrenia were evaluated in a randomized, placebo-controlled, multicenter study comprised of a 1-week titration period and a 3-week double-blind maintenance period (n=593).[562] Patients were randomized to iloperidone 24 mg, ziprasidone 160 mg (active control), or placebo daily. Iloperidone demonstrated significant reduction versus placebo on the PANSS score (primary outcome). Significant improvement versus placebo was also demonstrated with ziprasidone. Compared with ziprasidone, iloperidone was associated with lower rates of sedation, somnolence, extrapyramidal symptoms, akathisia, agitation, and restlessness; iloperidone was associated with higher rates of weight gain, tachycardia, orthostatic hypotension, dizziness, and nasal congestion. A similar amount of QT prolongation was observed with both active treatments, although no patient had a corrected QT interval of 500 msec or greater.

A second, 6-week, placebo-controlled trial compared 2 flexible dose ranges of iloperidone (12 to 16 mg/day and 20 to 24 mg/day) to placebo and an active comparator (risperidone) with a 1-week dose titration period on patients with schizophrenia (n=706).[563] The primary endpoint was change in BPRS total score after 6 weeks from baseline, and both iloperidone and risperidone were superior to placebo in this primary outcome. Following the first 2 weeks, risperidone and iloperidone appeared to have comparable efficacy.

A longer-term, treatment-withdrawal, placebo-controlled trial demonstrated the efficacy of iloperidone in maintenance of schizophrenia (n=303).[564] Following a 12-week open-label stabilization phase, patients were randomized to continue iloperidone (8 to 24 mg/day, administered as twice daily doses) or placebo for up to 26 weeks in the double-blind phase. An interim analysis determined that patients randomized to iloperidone had a statistically longer time to relapse or impending relapse than those randomized to placebo. The study was discontinued early due to evidence of efficacy.

lurasidone (Latuda) and quetiapine ER (Seroquel XR)

The relapse prevention efficacy of lurasidone versus quetiapine ER was evaluated for 12 months in adult patients (n=353) with chronic schizophrenia.[565] Study participants were first required to complete a 6-week placebo-controlled trial with treatment on lurasidone or quetiapine ER. Using a Kaplan-Meier analysis, it was determined that the probability of relapse for participants on lurasidone was 23.7% and 33.6% for quetiapine ER participants. The HR for probability of relapse was 0.728 (95% CI, 0.41 to1.295; log-rank p=0.28).The probability of hospitalization was estimated to be lower for the lurasidone group versus quetiapine ER (9.8% versus 23.1%; p=0.049). Lurasidone was also shown to be noninferior to quetiapine ER. The study did not measure superiority of lurasidone compared to quetiapine ER. Since discontinuation due to adverse events was similar between the 2 treatment groups (6.6% for lurasidone versus 4.7% for quetiapine ER), it was concluded that the relapse risk was not due to a difference in tolerability. Maintenance treatment with lurasidone was not associated with any significant effects on weight or metabolic parameters. This study was funded by the manufacturer of lurasidone.

Similarly designed studies by many of the authors of the above study with both placebo- and active-controls have demonstrated an improvement in neurocognitive performance with lurasidone over quetiapine ER; however, these trials were also funded by the manufacturer of lurasidone.[566,567]

lurasidone (Latuda) versus risperidone (Risperdal)

A randomized, double-blind, active-controlled long-term safety and tolerability study of lurasidone was conducted for 12 months in the treatment of schizophrenia.[568] A total of 628 clinically stable outpatients with schizophrenia were randomized to treatment with lurasidone 40 to 120 mg once daily or 2 to 6 mg of risperidone. Outcome measures included adverse events, vital signs, electrocardiogram (ECG), and laboratory tests. Secondary assessments included efficacy measures of psychopathology using PANSS and CGI-S scores. The 3 most frequent adverse events in the lurasidone group were nausea, insomnia, and sedation. The 3 most frequent adverse events in the risperidone group were increased weight, somnolence, and headache. The median endpoint change in prolactin was significantly higher for risperidone (p<0.001). A comparable improvement in efficacy measures was observed with both agents and the rates of relapse were similar. All-cause discontinuation rates were higher for lurasidone versus risperidone. This study was funded by the manufacturer of lurasidone.

lurasidone (Latuda) versus placebo in pediatrics

A 6-week, multicenter, randomized, double-blind, placebo-controlled evaluation established the efficacy of lurasidone for the treatment of schizophrenia in adolescents (13 to 17 years) (n=326).[569] Patients were randomized to either lurasidone 40 mg or 80 mg per day or to placebo. At both doses, lurasidone was superior to placebo in reduction of PANSS (the primary endpoint) and CGI-S scores at 6 weeks. Notably, no consistent differences were found between doses of lurasidone.

molindone versus olanzapine (Zyprexa) versus and risperidone (Risperdal)

A double-blind trial randomly assigned pediatric patients (ages 8 to 19 years) with early-onset schizophrenia and schizoaffective disorder to treatment with oral olanzapine (2.5 to 20 mg/day), risperidone (0.5 to 6 mg/day), or molindone (10 to 140 mg/day plus 1 mg/day of benztropine) for 8 weeks.[570] The primary outcome was response to treatment, defined as a CGI-I score of 1 or 2 and ≥ 20% reduction in PANSS total score. Of 119 patients randomly assigned to treatment, 116 patients

received at least 1 dose of treatment and thus were available for analysis. No significant differences were found among treatment groups in response rates (molindone: 50%; olanzapine: 34%; risperidone: 46%) or magnitude of symptom reduction. Olanzapine and risperidone were associated with significantly greater weight gain. Molindone was associated with more akathisia.

olanzapine (Zyprexa) versus quetiapine (Seroquel) versus risperidone (Risperdal) versus ziprasidone (Geodon) versus perphenazine

In phase 1 of the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) study, an NIMH-funded, double-blind study, 1,493 patients with schizophrenia were randomized to receive oral olanzapine (7.5 to 30 mg/day; mean dose 20.1 mg/day), quetiapine (200 to 800 mg/day; mean dose 543.4 mg/day), risperidone (1.5 to 6 mg/day; mean dose 3.9 mg/day), ziprasidone (40 to 160 mg/day; mean dose 112.8 mg/day), or the FGA, perphenazine (8 to 32 mg/day; mean dose 20.8 mg/day) for up to 18 months.[571] In the multicenter study, 74% of patients discontinued the study medication before 18 months. The time to discontinuation was significantly longer in the olanzapine group (9.2 months) than in the quetiapine (4.6 months; p<0.001) or risperidone (4.8 months; p=0.002) groups. No other comparisons between drugs regarding discontinuation were statistically significant. The PANSS and CGI improved similarly in all treatment groups. Time to discontinuation due to lack of efficacy was longer in the olanzapine group than in the perphenazine (p<0.001), quetiapine (p<0.001), or risperidone (p<0.001) groups. There was no significant difference between groups in time to discontinuation due to intolerable adverse effects. The duration of successful treatment was longer in the olanzapine group than in the quetiapine (p<0.001), risperidone (p=0.002), or perphenazine (p=0.013) groups, but not the ziprasidone group. The duration of successful treatment was longer in the risperidone group than the quetiapine group (p=0.021). No other between-group comparisons were statistically significant. The risk of hospitalization for exacerbation of schizophrenia (normalized for total patient-years of exposure) ranged from 0.29 for olanzapine to 0.66 for quetiapine. The rates of treatment discontinuation due to intolerability ranged from 10% for risperidone to 18% for olanzapine. A subsequent analysis evaluated the extent to which continuing to take the same antipsychotic that a patient had been on prior to the study, rather than switching to a new agent upon entry into the study, affected the time to discontinuation.[572] Results from the analysis indicate that rates of treatment discontinuation were lower for patients that continued their previous therapy than for those that changed their antipsychotic. Removal of data from patients continuing therapy attenuated the original study results, although the original pattern of these results remained the same.

Psychosocial functioning was assessed in the CATIE trial using the Quality of Life Scale.[573] Psychosocial functioning modestly improved for the one-third of phase 1 patients who reached the primary Quality of Life Scale analysis endpoint of 12 months (average effect size, 0.19 SD units). For several individual drugs, there were significant changes from baseline, but, overall, there were no significant differences among the agents. Results were similar at 6, 12, and 18 months.

In an effort to compare neurocognitive effects of several SGAs and a FGA, perphenazine, a randomized, double-blind study of patients with schizophrenia was conducted.[574] These patients were assigned to receive treatment with oral olanzapine, perphenazine, quetiapine, or risperidone for up to 18 months. This also included ziprasidone after its FDA approval, as reported previously in the CATIE study. From a cohort of 1,460 patients in the treatment study, 817 patients completed the neurocognitive testing immediately prior to randomization and after 2 months of treatment. The primary outcome was change in neurocognitive composite score after 2 months of treatment. Secondary outcomes included

neurocognitive composite score change at 6 months and 18 months after continued treatment and changes in neurocognitive domain. At 2 months, treatment resulted in small neurocognitive improvements for olanzapine ($p<0.002$), perphenazine ($p<0.001$), quetiapine ($p<0.001$), risperidone ($p<0.001$), and ziprasidone ($p<0.06$) with no significant differences between groups. These results differ from the majority of previous studies and may be due to such factors as more than twice the number of patients in the CATIE trial; lower relative doses of the FGA, perphenazine, used in the CATIE trial; and the broad inclusion and minimal exclusion criteria in the CATIE trial, such as inclusion of patients with comorbid conditions on concomitant medications and/or with current substance abuse. Results at 6 months were similar. After 18 months of treatment, neurocognitive improvement was greater in the perphenazine group than in the olanzapine and risperidone groups. Neurocognitive improvement predicted longer time to treatment discontinuation, independent from symptom improvement, in patients treated with quetiapine or ziprasidone.

Subjects with schizophrenia who had discontinued the SGA randomly assigned during phase 1 of the CATIE investigation were randomly reassigned to double-blind treatment with a different antipsychotic (oral olanzapine 7.5 to 30 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6 mg/day or ziprasidone 40 to 160 mg/day).[575] In the 444-patient study, the time to treatment discontinuation, the primary endpoint, was longer for patients treated with risperidone (7 months; 95% CI, 4.1 to 10 months) and olanzapine (6.3 months; 95% CI, 3.5 to 9.7 months) than with quetiapine (4 months; 95% CI, 3.1 to 4.8 months) and ziprasidone (2.8 months; 95% CI, 2.4 to 4.4 months). Among the 184 patients who discontinued their previous antipsychotic because of inefficacy, olanzapine was more effective than quetiapine and ziprasidone and risperidone was more effective than quetiapine. There were no significant differences between antipsychotics among the 168 patients who discontinued their previous treatment because of intolerability.

Subjects with schizophrenia (n=114) who had been randomly assigned to and then discontinued perphenazine in phase 1 of the CATIE study were reassigned randomly to double-blinded treatment with oral olanzapine (n=38), quetiapine (n=38), or risperidone (n=38).[576] The primary goal was to determine whether there were differences among these 3 treatments in effectiveness, as measured by time to discontinuation for any reason. Secondary outcomes included reasons for treatment discontinuation and measures of drug tolerability. The time to treatment discontinuation was longer for patients treated with quetiapine and olanzapine than with risperidone. No significant differences existed between treatments related to discontinuation due to inefficacy, intolerability, or patient decision.

Phase 4 of the CATIE study compared the response to antipsychotic treatment between patients with and without tardive dyskinesia (TD) and examined the course of TD.[577] This analysis compared 200 patients with DSM-IV-defined schizophrenia and TD and 997 patients without TD, all of whom were randomly assigned to receive 1 of 4 SGAs as used in previous phases (olanzapine, quetiapine, risperidone, and ziprasidone). The primary clinical outcome measure was time to all-cause treatment discontinuation, and the primary measure for evaluating the course of TD was change from baseline in Abnormal Involuntary Movement Scale (AIMS) score. Kaplan-Meier survival analysis and Cox proportional hazards regression models were used to compare treatment discontinuation between groups. Changes in PANSS and neurocognitive scores were compared using mixed models and analysis of variance. Treatment differences between drugs in AIMS scores and all-cause discontinuation were examined for those with TD at baseline. Percentages of patients meeting criteria for TD post-baseline or showing changes in AIMS scores were evaluated with chi-square tests. Time to treatment

discontinuation for any cause was not significantly different between the TD and non-TD groups (chi-square [1] = 0.11, p=0.743). Changes in PANSS scores were not significantly different (p=0.366), but patients with TD showed less improvement in neurocognitive scores (p=0.011). Among patients with TD, there were no significant differences between drugs in the decline in AIMS scores (p=0.811); 55% met criteria for TD at 2 consecutive visits post-baseline, 76% met criteria for TD at some or all post-baseline visits, 24% did not meet criteria for TD at any subsequent visit, 32% showed 50% or greater decrease in AIMS score, and 7% showed a 50% or greater increase in AIMS score. The authors concluded patients with schizophrenia with and without TD were similar in time to discontinuation of treatment for any cause and improvement in psychopathology, but differed in neurocognitive response. There were no significant differences between treatments in the course of TD, with most patients showing either persistence of or fluctuation in observable symptoms.

olanzapine (Zyprexa), quetiapine (Seroquel), or risperidone (Risperdal) versus clozapine

The CATIE investigation was continued in order to compare clozapine to other SGAs in patients who had discontinued the newer agents during phase 1 CATIE study.[578] Phase 2 of the study consisted of 99 patients who had inadequate response to treatment with oral olanzapine, quetiapine, risperidone, or ziprasidone during phase 1 or 1b. Patients were randomly assigned to open-label treatment with clozapine (n=49) or blinded treatment with another newer SGA not previously administered in the trial (olanzapine [n=19], quetiapine [n=15], or risperidone [n=16]). Results indicated that time until treatment discontinuation for any reason was significantly longer for clozapine (median = 10.5 months; 95% CI, 7.3 to 16.1 months) than for quetiapine (median = 3.3 months; 95% CI, 1 to 4.9 months), risperidone (median = 2.8 months; 95% CI, 1.1 to 4 months), or olanzapine (median = 2.7 months; 95% CI, 1.9 to 11.9 months). Time to discontinuation because of inadequate therapeutic effect was longer for clozapine (median 13.7 months) than for olanzapine, quetiapine, or risperidone. At 3-month assessments, PANSS total scores had decreased more in patients treated with clozapine than in patients treated with quetiapine or risperidone, but not olanzapine. Treatment discontinuations in 2 patients treated with clozapine occurred with the development of agranulocytosis and eosinophilia. Clozapine demonstrated responsiveness in patients who had failed other SGAs, but its use requires safety monitoring for blood dyscrasias.

olanzapine (Zyprexa) versus risperidone (Risperdal)

An international, multicenter, double-blind, parallel-group, 28-week prospective study was conducted with 339 patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder.[579] The study indicated that both oral olanzapine and risperidone were safe and effective in the management of psychotic symptoms. However, olanzapine demonstrated greater efficacy in negative symptoms and overall response rate (≥ 40% decrease in the PANSS total score). A greater proportion of the olanzapine-treated than risperidone-treated patients maintained response at 28 weeks based on Kaplan-Meier survival curves. The incidences of EPS, hyperprolactinemia, and sexual dysfunction were lower in olanzapine-treated than risperidone-treated patients. In addition, fewer adverse events were reported by olanzapine-treated patients than by their risperidone-treated counterparts. This study was performed by the manufacturer of olanzapine. Notably, neither agent is approved for schizophreniform disorder or schizoaffective disorder.

In a multicenter, double-blind study, 150 patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder were randomized to oral olanzapine 10 to 20 mg/day (mean dose, 17.7 mg/day) or risperidone 4 to 12 mg/day (mean dose, 7.9 mg/day) for a maximum of 28 weeks.[580]

Response, defined as a 40% improvement in PANSS, was more likely to be maintained with olanzapine than with risperidone (p=0.048). A smaller proportion of olanzapine-treated patients required anticholinergic therapy compared with risperidone-treated patients (25.3% versus 45.3%; p=0.016). Again, neither agent is approved for schizophreniform disorder or schizoaffective disorder.

In a double-blind study, 377 patients with schizophrenia or schizoaffective disorder were randomly assigned to receive risperidone (mean dose 4.8 mg/day) or olanzapine (mean dose 12.4 mg/day) for 8 weeks.[581,582] Total PANSS scores, as well as PANSS negative and positive subscales, were improved in both groups; comparison of individual factors found no significant differences at endpoint. Cognitive function, assessed with a focused cognitive assessment battery, showed no differences in the effects of the 2 drugs. Correcting for the effects of anticholinergic treatment did not alter the magnitude of cognitive effects, indicating that these agents have a direct effect on cognitive deficits in schizophrenia. Seventy-five percent of the participants completed the trial with no between-treatment differences in the proportion of dropouts. Similar proportions of the risperidone and olanzapine groups reported EPS (24% and 20%, respectively). Severity of EPS was low in both groups with no between-group differences. An increase in body weight of at least 7% was seen in 27% of olanzapine participants and 12% of risperidone participants. Neither agent is approved for schizoaffective disorder.

olanzapine (Zyprexa) versus ziprasidone (Geodon)

In a multicenter, double-blind, parallel-group, 28-week study, 548 patients with schizophrenia were randomly assigned to treatment with oral olanzapine (10 to 20 mg/day) or ziprasidone (80 to 160 mg/day).[583] The study was completed by more olanzapine-treated patients (59.6%) than ziprasidone-treated patients (42.4%; p<0.05). At 28 weeks, the olanzapine-treated patients showed more improvement than the ziprasidone-treated patients on the PANSS (the primary efficacy measure) and all subscales and on the CGI-I and CGI-S. The responder rate was higher for olanzapine than for ziprasidone. Extrapyramidal symptoms were not significantly different between groups. There was a notable difference between the 2 drugs on the effect on weight with the olanzapine group increasing by a mean 3.1 kg, and the ziprasidone group decreasing by a mean 1.1 kg. Fasting lipid profiles were better in the ziprasidone group; there was no significant difference in fasting glucose level. This study was conducted by the manufacturer of olanzapine.

An 8-week, double-blind, parallel-group, randomized, controlled multicenter trial of 76 patients with schizophreniform disorder, schizophrenia, or schizoaffective disorder (diagnosis less than 5 years), and a maximum lifetime antipsychotic treatment of less than 16 weeks, participated in the study to compare the efficacy and tolerability of ziprasidone (80 to 160 mg daily) and olanzapine (10 to 20 mg daily) in patients with recent-onset disease.[584] Efficacy of ziprasidone and olanzapine was measured using PANSS, CGI, the Calgary Depression Scale for Schizophrenia (CDSS), and the Heinrich Quality of Life Scale (HQLS). Tolerability assessments included laboratory assessments, body weight, and electroencephalogram (EEG). Olanzapine (n=34) and ziprasidone (n=39) showed equal efficacy as measured by the various scales; however, mean weight gain was significantly higher in the olanzapine group (6.8 versus 0.1 kg; p<0.001). Ziprasidone was associated with decreasing levels of triglycerides, cholesterol, and transaminases, while these parameters increased in the olanzapine group (all p values <0.05). There were no significant differences in fasting glucose and prolactin levels or in cardiac or sexual side effects. Patients on ziprasidone used biperiden for extrapyramidal side effects more frequently (p<0.05). The results of this study indicate that ziprasidone and olanzapine have comparable therapeutic efficacy but differ in their side effect profile. However, there is a risk of a type II error due

to the limited sample size. This study was sponsored by the manufacturer of ziprasidone. Neither agent is approved for schizophreniform disorder or schizoaffective disorder.

olanzapine (Zyprexa) versus placebo in pediatrics

The safety and efficacy of oral olanzapine were evaluated in a 6-week, double-blind, flexible-dose, placebo-controlled, randomized acute treatment trial of adolescents (ages 13 to 17 years) with schizophrenia (n=107).[585] After 6 weeks, olanzapine demonstrated a greater reduction Brief Psychiatric Rating Scale for Children (BPRS-C) total score compared to placebo.

paliperidone ER (Invega) versus placebo

In a double-blind study, 630 patients with schizophrenia were randomized to receive paliperidone ER 6 mg, 9 mg, or 12 mg, olanzapine 10 mg (active-control), or placebo once daily for 6 weeks.[586] The primary endpoint was change in total PANSS score from baseline. Improvement in mean total PANSS scores was significantly greater with paliperidone ER than placebo at all time points starting at day 4 for the 12 mg dosage ($p<0.01$) and day 8 for the lower doses ($p<0.05$). A greater number of patients receiving active treatment completed the study. In a similar study, 618 patients with schizophrenia were randomized to receive paliperidone ER 3 mg, 9 mg, 15 mg, oral olanzapine 10 mg (active-control), or placebo once daily.[587] Significant improvement in PANSS total scores were noted with all doses of paliperidone ER from day 4 forward. In a third study of similar design, 444 patients with schizophrenia were randomized to receive fixed daily doses of paliperidone ER 6 mg or 12 mg, olanzapine 10 mg (active-control), or placebo for 6 weeks.[588] In the study, significant improvement, compared to placebo, was noted from day 4 forward for the lower dose of paliperidone ER and from day 15 forward for the higher dose of paliperidone ER.

Paliperidone (Invega) also demonstrated acute efficacy in adults with schizoaffective disorder in two, 6-week, placebo-controlled trials.[589] In both studies, paliperidone was used as either monotherapy or as adjunctive therapy with mood stabilizers and/or antidepressants. In Study 1, patients were randomized to flexibly dose paliperidone (3 to 12 mg/day) or placebo (n=211). In Study 2, patients were randomized to paliperidone 3 to 6 mg, paliperidone 9 to 12 mg, or placebo (n=203). In Study 1, paliperidone demonstrated superiority over placebo in PANSS improvement, the primary outcome in both trials; however, in Study 2, only the higher dosage range (9 to 12 mg) demonstrated superiority over placebo in PANSS improvement. Improvements with paliperidone over placebo were also seen in Study 1 and the higher dose group of Study 2 based on the Young Mania Rating Scale (YMRS) and Hamilton Depression Rating Scale (HAM-D) measures.

paliperidone ER (Invega) versus placebo in pediatrics

A 6-week, double-blind, parallel-group study, randomized adolescents (n=201), 12 to 17 years old with schizophrenia, to receive either placebo or 1 of 3 weight-based, fixed doses of oral paliperidone ER (1.5, 3, or 6 mg) once-daily.[590,591] Paliperidone ER at doses of 3 to 12 mg demonstrated superiority over placebo in PANSS score improvement after 6 weeks. Although doses within this broad range were shown to be effective, there was no clear benefit to efficacy at the higher doses.

quetiapine (Seroquel) versus risperidone (Risperdal)

In a double-blind study, 673 patients with schizophrenia were randomized to receive quetiapine 200 to 800 mg/day (mean dose 525 mg/day) or risperidone 2 to 8 mg/day (mean dose 5.2 mg/day) for 8 weeks.[592] At the conclusion of the study, there were no significant differences between groups in

PANSS total scores, response rates, or CGI. There was a significantly greater improvement in the PANSS positive subscale in the risperidone group (p=0.03). The rate of EPS was higher with risperidone (22%) than with quetiapine (13%; p<0.01). Somnolence was more common with quetiapine (25%) than with risperidone (20%; p=0.04). Prolactin levels increased with risperidone and decreased with quetiapine (p<0.001 for comparison of change in prolactin levels). This study was performed by the manufacturer of quetiapine.

quetiapine (Seroquel) versus quetiapine ER (Seroquel XR)

A double-blind, double-dummy study was conducted to evaluate the efficacy and safety of switching patients with clinically stable schizophrenia from twice daily quetiapine immediate-release (IR) to the same dose of quetiapine once daily extended release (XR).[593] All patients initially received quetiapine IR 400 to 800 mg twice daily for 4 weeks and were then randomized to once daily equivalent dose of quetiapine ER or maintained on quetiapine IR for 6 weeks. The primary efficacy variable was the proportion of patients who discontinued treatment due to lack of efficacy or who had at least a 20% increase in their positive or negative symptom scale scores. In total, 497 patients were randomized to either the XR formulation (n=331) or the IR formulation (n=166). Non-inferiority was not demonstrated for the modified intention to treat population; however, non-inferiority was demonstrated for the per-protocol population (XR=5.3%, IR=6.2%; p=0.0017). No serious adverse effects were demonstrated for either of the formulations. The authors concluded that efficacy was maintained without compromising safety and/or tolerability when switching patients with stable schizophrenia from the twice daily IR formulation to the once daily XR formulation of quetiapine.

quetiapine (Seroquel) versus placebo in pediatrics

In a 6-week, double-blind, placebo-controlled trial, adolescents (n=222), 13 to 17 years old with schizophrenia were randomized to quetiapine 400 or 800 mg per day, or placebo.[594] Both doses of quetiapine were superior to placebo in reducing PANSS total score.

quetiapine ER (Seroquel XR) versus placebo in pediatrics

The safety and efficacy of quetiapine ER in adolescents with schizophrenia were supported by a 6-week, double-blind, placebo-controlled trial with quetiapine.[595] Quetiapine at doses of 400 and 800 mg/day provided significant improvements in symptoms associated with schizophrenia in adolescent patients (n=220) aged 13 to 17 years, including the primary efficacy measure of PANSS total score change. The adverse event profile of quetiapine was well tolerated and similar to what is seen in adult schizophrenia patients.

risperidone (Risperdal) versus ziprasidone (Geodon)

Patients with an acute exacerbation of schizophrenia or schizoaffective disorder were randomly assigned in a double-blind fashion to oral ziprasidone 40 to 80 mg twice daily or risperidone 3 to 5 mg twice daily for 8 weeks.[596] Primary efficacy measures were PANSS total score and CGI-S score. In the 296-patient study, equivalence was demonstrated in the 2 primary efficacy measurements, PANSS and CGI-S, as well as in PANSS negative subscale scores, BPRS, PANSS total, and CGI-I responder rates. Both agents were well tolerated. Risperidone exhibited significantly greater movement disorder burden (p<0.05), higher incidences of prolactin elevation, and clinically relevant weight gain. Study dosing was above current recommendations for some risperidone-treated patients (mean dose 7.4 mg/day) and below current recommendations for some ziprasidone-treated patients (mean dose 114.2 mg/day).

Both agents equally improved psychotic symptoms, and both were generally well tolerated. In a 44-week extension study, patients (n=139) continued their current treatment.[597] There were no significant differences in PANSS and CGI-S scores at study endpoint. Ziprasidone patients showed greater MADRS improvement in depressive symptoms compared to risperidone patients (p<0.05). Risperidone was associated with more EPS, prolactin, and weight gain adverse events than ziprasidone. The median doses were 120 mg/day for ziprasidone and 8 mg/day for risperidone. Neither agent is approved for schizoaffective disorder.

ziprasidone (Geodon) versus clozapine (Clozaril)

An 18-week, randomized, double-blind trial evaluated ziprasidone as an alternative to clozapine in treatment-refractory schizophrenia patients.[598] Patients (n=147) had a history of resistance and/or intolerance to at least 3 acute cycles with different antipsychotics given at therapeutic doses, PANSS score ≥ 80, and CGI-S score ≥ 4. Patients were randomized to ziprasidone 80 to 160 mg daily or clozapine 250 to 600 mg daily. Baseline-to-endpoint decreases in PANSS total scores were similar in the ziprasidone (-25; 95% CI, -30.2 to -19.8) and clozapine groups (-24.5; 95% CI, -29.7 to -19.2). A progressive and significant reduction from baseline in PANSS total score was observed from day 11 in both study arms. There were also significant improvements for PANSS subscales, CGI-S, CGI-I, CDSS, and GAF without between-drug differences. The 2 treatment groups had similar rates of early discontinuations due to adverse effects, which were of similar severity in the 2 groups. Ziprasidone, but not clozapine, did show a significant reduction of Simpson-Angus Scale (SAS) and AIMS scores. Ziprasidone also had a more favorable metabolic adverse effect profile.

ziprasidone (Geodon) versus haloperidol (Haldol)

In a 6-week, multicenter, open-label, parallel-group study, patients with schizophrenia or schizoaffective disorder were randomized to ziprasidone (IM up to 3 days, then oral 40 to 80 mg twice daily) or haloperidol lactate (IM up to 3 days, then oral 5 to 20 mg daily).[599] Following IM treatment, patients receiving ziprasidone (n=427) showed significantly improved BPRS total scores compared with those receiving haloperidol (n=138, p<0.0018). At endpoint (6-weeks), there were no significant between-group differences in BPRS total scores. There was a significantly greater improvement in BPRS negative subscale scores in ziprasidone patients, both at the end of IM treatment (p<0.0001) and at study endpoint (p<0.0001). Haloperidol patients exhibited significantly greater increases in EPS at the end of IM treatment and at endpoint (p<0.0001). Neither agent is approved for schizoaffective disorder.

Long-Acting Injectable Antipsychotics for Schizophrenia, Schizoaffective Disorder, and/or Bipolar Disorder

In addition to the comparative trials below, paliperidone palmitate (Invega Sustenna) has also demonstrated superiority over placebo in patients with schizophrenia as monotherapy (short- and long-term) and schizoaffective disorder (maintenance treatment) as both monotherapy and adjunctive therapy.[600] Likewise, risperidone microspheres (Risperdal Consta) have also demonstrated superiority over placebo in patients with schizophrenia in clinical trials.[601]

aripiprazole (Abilify Maintena) versus placebo

The efficacy of aripiprazole intramuscular (IM) depot injection for the treatment of schizophrenia was evaluated in a 12-week, double-blind, placebo-controlled, randomized trial in 339 acutely relapsed

adults with schizophrenia (based on DSM-IV-TR criteria).[602] Patients were randomized to 300 to 400 mg aripiprazole IM depot or placebo on days 0, 28, and 56. At Week 10, aripiprazole IM depot was superior to placebo in PANSS total score improvement. Superior improvements in CGI-S were also seen with aripiprazole compared to placebo.

A longer-term, placebo-controlled, double-blind, randomized, treatment withdrawal trial was also used to establish the efficacy of aripiprazole depot IM in the maintenance treatment of adults with schizophrenia (based on DSM-IV-TR criteria).[603,604] Following a 4 to 6 week open-label oral conversion and subsequent 12-week stabilization phase, 403 patients were randomized to continue aripiprazole depot IM (300 to 400 mg monthly) or to placebo for 52 weeks. The primary endpoint was time to relapse based on clinical measures or hospitalization. The study was terminated early because efficacy of aripiprazole was demonstrated in the preplanned interim analysis. Improvements in CGI-S and PANSS total scores were maintained with aripiprazole IM depot treatment but worsened with placebo.

The efficacy of long-acting aripiprazole IM for the treatment of bipolar I disorder was established in a double-blind, placebo-controlled, 52-week randomized withdrawal study in patients currently experiencing a manic episode.[605] Patients were first stabilized on oral aripiprazole and long-acting aripiprazole 400 mg once monthly and then randomized to either continue long-acting aripiprazole or placebo (n=266). The primary end point was the time to recurrence of any mood episode. Compared with placebo, aripiprazole delayed the time to episode recurrence (HR, 0.45; 95% CI, 0.3 to 0.68; p<0.0001). Notably, 48.1% of patients in the aripiprazole group and 28.6% of those in the placebo group completed the study.

aripiprazole lauroxil (Aristada) versus placebo

The efficacy and safety of aripiprazole lauroxil were evaluated in a phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled trial.[606,607] Adult patients ages 18 to 70 years, meeting DSM-IV-TR criteria for schizophrenia with a relapse or exacerbation within the past 2 months, were randomized to gluteal IM aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg, or placebo once monthly for 12 weeks (n=623). Patients with a prior inadequate response to oral aripiprazole were excluded. Significant differences at day 85 were seen compared to placebo in PANSS score (primary outcome) and CGI-I scale. Approval of subsequent dosing regimens was based on pharmacokinetic analyses comparing the dosing regimens to those used monthly in this trial.

fluphenazine decanoate versus haloperidol decanoate (Haldol Decanoate)

An 8-month, parallel-group, double-blind trial comparing haloperidol decanoate with fluphenazine decanoate in the maintenance treatment schizophrenia was performed in 72 outpatients.[608] The initial injection interval was based on pretrial maintenance treatment with fluphenazine. The dosage equivalency of haloperidol decanoate (75 mg) to fluphenazine decanoate (25 mg) used was 3:1, and injections were given every 2, 3, or 4 weeks. No statistically significant differences in therapeutic effect were found between the drugs. Both drugs had a similar EPS profile.

A 20-week, double-blind study compared the efficacy and safety of haloperidol decanoate and fluphenazine decanoate, both given every 4 weeks, in 51 schizophrenia patients.[609] The mean dose of fluphenazine decanoate was 84 mg compared to 122 mg for the haloperidol decanoate group, suggesting a potency ratio of 1:1.4. Injections were administered every 4 weeks. The CPRS subscale for schizophrenic symptoms and the subscale for depression symptoms each showed a statistically significant improvement (p<0.05) for the haloperidol decanoate group after 20 weeks. No significant

between-group differences were found in the incidence of EPS at week 20. More patients on fluphenazine decanoate gained weight than patients on haloperidol decanoate, but the difference was not statistically significant.

olanzapine (Zyprexa Relprevv) versus placebo or oral olanzapine (Zyprexa)

Short-term efficacy of ER IM olanzapine was established in an 8-week placebo-controlled trial in 404 adult patients with schizophrenia (based on DSM-IV or DSM-IV-TR criteria).[610] Patients were randomized to olanzapine ER IM (210 or 200 mg every 2 weeks or 405 mg every 4 weeks) or to placebo. Olanzapine ER IM demonstrated superiority over placebo in change in total PANSS score from baseline, the primary endpoint.

A longer-term trial compared oral olanzapine (stabilized dose) to olanzapine ER IM 150 mg or 300 mg IM every 2 weeks, 45 mg (reference dose), or 405 mg IM every 4 weeks in 1,065 outpatients with schizophrenia who had been on a stable oral olanzapine regimen.[611,612] At 24 weeks, patients receiving oral or standard dosed ER IM olanzapine had a longer time to exacerbation of symptoms based on increases in the BPRS compared to the reference dose.

paliperidone palmitate (Invega Sustenna) versus haloperidol decanoate (Haldol Decanoate)

A randomized, double-blind, multicenter clinical trial was conducted in adult patients (n=311) diagnosed with schizophrenia or schizoaffective disorder who were clinically assessed to be at risk of relapse and likely to benefit from a long-acting injectable antipsychotic.[613] The primary endpoint was to compare the effectiveness of paliperidone palmitate with haloperidol decanoate. There was no statistically significant difference in the rate of efficacy failure for paliperidone palmitate compared with haloperidol decanoate (adjusted HR, 0.98; 95% CI, 0.65 to 1.47). The number of participants who experienced efficacy failure was 49 (33.8%) in the paliperidone palmitate group and 47 (32.4%). The paliperidone palmitate group was associated with more weight gain and greater increases in serum prolactin, whereas haloperidol decanoate was associated with more akathisia.

paliperidone palmitate (Invega Sustenna) versus oral antipsychotics

The Paliperidone Palmitate Research in Demonstrating Effectiveness (PRIDE) study was a prospective, open-label, randomized, 15-month study comparing long-acting injectable paliperidone palmitate and oral antipsychotic medications in 450 subjects (444 subjects were included in the intent-to-treat population) with schizophrenia (according to DSM-IV criteria).[614] Subjects were randomly assigned to once-monthly paliperidone palmitate injections or daily oral antipsychotics (randomly assigned from 7 acceptable, prespecified oral antipsychotics) for 15 months. The primary endpoint was time to first treatment failure, defined as arrest/incarceration; psychiatric hospitalization; suicide; treatment discontinuation or supplementation due to inadequate efficacy, safety, or tolerability; or increased psychiatric services to prevent hospitalization. Time to first treatment failure was determined by a blinded event-monitoring board and analyzed with the Kaplan-Meier method. Paliperidone palmitate was associated with significant delay in time to first treatment failure versus oral antipsychotics (hazard ratio, 1.43; 95% CI, 1.09 to 1.88; log rank p=0.011). Observed treatment failure rates over 15 months were 39.8% and 53.7%, respectively. Arrest/incarceration and psychiatric hospitalization were the most common reasons for treatment failure in the paliperidone palmitate and oral antipsychotic groups (21.2% versus 29.4% and 8% versus 11.9%, respectively). The 5 most common treatment-emergent adverse events for the paliperidone palmitate treatment group were injection site pain (18.6%), insomnia (16.8%), weight increase (11.9%), akathisia (11.1%), and anxiety (10.6%). Once-

monthly paliperidone palmitate demonstrated superiority compared to oral antipsychotics in delaying time to treatment failure.

paliperidone palmitate (Invega Trinza) versus placebo

A long-term, double-blind, placebo-controlled randomized-withdrawal trial was conducted on patients who met DSM-IV-TR criteria for schizophrenia to assess time to relapse.[615,616] Acute or stable patients were eligible, but patients currently receiving the 39 mg dose of 1-month paliperidone palmitate were ineligible. Three treatment periods included the following: (1) a 17-week flexible dose open-label stabilization period including a total of 506 patients with individualized 1-month paliperidone palmitate dosing to achieve a PANSS score of < 70 to demonstrate clinical stability, (2) a 12-week open-label stabilization period including a total of 379 patients to achieve a PANSS score of < 70 and scores of ≤ 4 for 7 specific PANSS items using 3-month paliperidone palmitate (as dosed as 3.5 times the last dose of the 1-month formulation used in the open-label phase), (3) a variable length double-blind treatment period including a total of 305 stabilized patients randomized to Invega Trinza (same dose as open-label phase), or (4) placebo until relapse, early withdrawal, or the end of the study. The primary efficacy variable was time to first relapse. The study ended early due to Invega Trinza demonstrating a statistically significant longer time to relapse than placebo.

risperidone (Risperdal Consta) versus oral olanzapine (Zyprexa)

To compare risperidone IM and oral olanzapine, 377 patients with schizophrenia or schizoaffective disorder were randomized to receive risperidone IM 25 mg or 50 mg every 14 days or oral olanzapine 5 to 20 mg daily in an open-label trial.[617] Over 13 weeks, risperidone IM was at least as effective as oral olanzapine. In the 12-month phase, significant improvements in the PANSS total and factor scores from baseline were seen in both groups of patients. Both treatments were well tolerated. A 2-year observational study of risperidone IM and various oral SGAs concluded that risperidone IM showed greater improvement in treatment retention and clinical symptoms of schizophrenia.[618] Neither agent is approved for the treatment of schizoaffective disorder.

risperidone (Risperdal Consta) versus oral antipsychotics

A 3-year, open-label, parallel-group, randomized controlled study of 369 patients with schizophrenia or schizoaffective disorder in the Veterans Affairs (VA) system was conducted to determine if long-acting injectable risperidone improves adherence to treatment and outcomes in schizophrenia.[619] Treatments were not blinded since giving placebo injections to the comparison group would interfere with the goal of comparing the acceptability of 2 different methods of medication administration. However, the endpoints were blindly rated. Patients who met the initial diagnosis criteria, as well as having a hospitalization within the previous 2 years or at imminent risk for hospitalization, were randomized to receive long-acting injectable risperidone 25 to 50 mg every 2 weeks or a psychiatrist's choice of an oral antipsychotic. The primary endpoint was hospitalization in a psychiatric hospital. Symptoms, quality of life, and functioning were assessed in blinded videoconference interviews. Of 369 participants, 40% were hospitalized at randomization, 55% were hospitalized within the previous 2 years, and 5% were at risk for hospitalization. The rate of hospitalization after randomization was not significantly lower among patients who received long-acting injectable risperidone than among those who received oral antipsychotics (39% after 10.8 months versus 45% after 11.3 months, respectively; HR, 0.87; 95% CI, 0.63 to 1.2). Psychiatric symptoms, quality of life, scores on the Personal and Social Performance scale of global functioning, and neurologic side effects were not significantly improved

with long-acting injectable risperidone as compared with control treatments. Patients who received long-acting injectable risperidone reported more adverse events at the injection site and more extrapyramidal symptoms. The authors concluded that long-acting injectable risperidone was not superior to a psychiatrist's choice of oral treatment in patients with schizophrenia and schizoaffective disorder who were hospitalized or at high risk for hospitalization, and it was associated with more local injection-site and extrapyramidal adverse effects. This study was supported by the VA Cooperative Studies Program and the manufacturer of long-acting injectable risperidone. Risperidone (Risperdal Consta) is not approved for the treatment of schizoaffective disorder.

risperidone (Risperdal Consta) versus oral risperidone (Risperdal)

A 12-month, randomized trial compared risperidone IM to oral risperidone in early course schizophrenia in adults at a single-center university clinic in Los Angeles (***n*=**86).[620] Patients with recent illness onset and a diagnosis of schizophrenia, schizoaffective, or schizophreniform disorder were randomized to open-label oral risperidone daily (mean, 3.6 mg/day; range, 1 to 7.5 mg/day) or risperidone IM every 2 weeks (mean, 26.3; range, 12.5 to 37.5) following a lead-in period with oral risperidone (variable doses). Patients were also randomized to 2 different psychosocial treatments: either cognitive remediation or healthy-behaviors training. The primary outcome was time to exacerbation or relapse identified by increases on the BPRS score assessed every 2 weeks. Psychiatric hospitalizations were also assessed. Risperidone IM offered an advantage over oral risperidone in exacerbation or relapse (5% versus 33%, respectively; $p<0.001$; relative risk reduction, 84.7%). No differences were seen based on psychosocial treatment ($p=0.6$). Hospitalizations were also lower with IM risperidone than with oral risperidone (5% versus 18.6%, respectively; $p=0.05$). While the population size was limited, relapse occurred during the first 6 months with oral risperidone and during months 4 to 8 with injectable risperidone.

risperidone intramuscular (Risperdal Consta) versus placebo

The efficacy of risperidone microspheres as monotherapy for the maintenance treatment of bipolar disorder was evaluated in a multicenter, double-blind, placebo-controlled study in 501 adults with bipolar I disorder (based on DSM-IV criteria).[621] Patients were treated during an open-label 26-week phase with risperidone microspheres (12.5 to 50 mg) and were subsequently randomized to continue treatment or switch to placebo in a double-blind treatment withdrawal phase. The primary endpoint was time to relapse for any mood episode (manic, hypomanic, mixed, or depressed). Time to relapse was significantly longer with risperidone microspheres compared to placebo.

The efficacy of risperidone microspheres as adjunctive therapy with lithium or valproate for the maintenance treatment of bipolar disorder was evaluated in a multicenter, double-blind, placebo-controlled study in 240 adults with bipolar I disorder (based on DSM-IV criteria).[622] Patients were treated during an open-label 16-week phase with risperidone microspheres (25 to 50 mg) with background mood stabilizers, antidepressants, and/or anxiolytics and were subsequently randomized to continue treatment or switch to placebo in a double-blind, 52-week, treatment withdrawal phase. The primary endpoint was time to relapse for any mood episode (manic, hypomanic, mixed, or depressed). Time to relapse was significantly longer with risperidone microspheres compared to placebo.

risperidone subcutaneous (Perseris) versus placebo

An 8-week, randomized, double-blind study compared the efficacy and safety of risperidone SC 90 mg or 120 mg, or placebo in adults experiencing acute exacerbations of schizophrenia.[623] Baseline PANSS score were 80 to 120 at screening, at which time all patients received 2 doses of oral risperidone 0.25 mg given 24 hours apart to establish tolerability. All patients were placed in an inpatient setting, if not already, and tapered off their current antipsychotic treatment. Patients were then given their randomized dose of risperidone SC 90 mg (n=111) or 120 mg (n=114) or placebo (n=112) every 4 weeks for 2 doses. No additional oral risperidone was allowed. At day 57, SC risperidone 90 mg and 120 mg resulted in significant improvement compared to placebo in mean change in PANSS score from baseline (-19.9 and -23.6 versus -13.4, respectively). Both risperidone doses also demonstrated significant improvement in CGI-S scores versus placebo.

Psychosis Associated with Parkinson's Disease

pimavanserin (Nuplazid) versus placebo

A 6-week, double-blind study assessed the efficacy of pimavanserin for the treatment of psychosis associated with Parkinson's disease.[624,625] Included patients were 40 years of age or older with a clinical diagnosis of idiopathic PD with a minimum duration of 1 year and psychotic symptoms that developed after the diagnosis of PD was established and included hallucinations (visual and/or auditory) and/or delusions and symptoms severe enough to warrant treatment (n=199). Non-pharmacologic psychosocial therapy was also used during the lead-in period to exclude patients who responded to non-drug modalities. Patients were randomly assigned to pimavanserin 34 mg or placebo once daily. The primary efficacy measure was the Scale for the Assessment of Positive Symptoms-Parkinson's Disease (SAPS-PD) which is a 9-item scale (a subset of the SAPS 20-item scale) that measured the domains of hallucinations and delusions (negative change indicates improvement in symptoms). Pimavanserin was associated with a 37% improvement in SAPS-PD (-5.79 change from baseline) compared to 14% for placebo (-2.73 change; p=0.001). Improvements in both hallucinations and delusions were reported. Compared to placebo, pimavanserin was associated with greater improvements in CGI-I and CGI-S. No effect on motor function compared to placebo was reported for pimavanserin based on UPDRS score.

Tourette's Disorder

aripiprazole (Abilify)

The safety and efficacy of aripiprazole were evaluated in 2 placebo-controlled trials in pediatric patients with Tourette's disorder: an 8-week study (ages 7 to 17 years; n=133) and a 10-week study (ages 6 to 18 years).[626] In both trials, aripiprazole demonstrated statistically significantly improved scores on the Yale Global Tic Severity Scale Total Tic score (YGTSS-TTS) and Clinical Global Impressions Scale for Tourette's Syndrome (CGI-TS) scales (8-week study only) compared to placebo.

META-ANALYSES

Bipolar Disorder

A meta-analysis of the efficacy and safety of second generation antipsychotics (SGAs) in the treatment of acute mania was conducted based on randomized, controlled trials comparing SGAs with placebo, FGAs, or mood stabilizers found in the PsiTri and MEDLINE databases.[627] Data on efficacy, global dropout, dropout due to adverse events, dropout due to inefficacy, weight gain, rate of somnolence, and EPS were extracted and combined in meta-analysis. A total of 24 studies with 6,187 patients were included. The SGAs were more efficacious than placebo. The addition of antipsychotic agents to mood stabilizer treatment was more effective than treatment with mood stabilizers alone. The SGAs demonstrated efficacy comparable with that of mood stabilizers. Some SGAs seemed to induce more extrapyramidal symptoms than placebo. The SGAs were associated with higher rates of somnolence than placebo.

A meta-analysis to systematically review the effectiveness of co-therapy compared with monotherapy for patients with bipolar mania was conducted using data on mania outcomes, withdrawals, extrapyramidal symptoms, and weight gain extracted from randomized controlled trials retrieved from MEDLINE, Embase, Psychinfo, the Cochrane Library, and reference lists.[628] Each trial was assessed for susceptibility to bias. Pooled effect estimates were summarized as relative risks (RR) or differences in mean values (MD), where appropriate. Eight eligible studies were included with 1,124 participants. Significant reductions in mania based on the Young Mania Rating Scale (YMRS) were shown for haloperidol, oral olanzapine, oral risperidone, and quetiapine as co-therapy compared with monotherapy with a mood stabilizer. For SGAs combined, the pooled difference in mean scores was 4.41 (95% CI, 2.74 to 6.07). Significantly more participants on co-therapy met the response criterion (≥ 50% reduction in YMRS score). With some drugs, co-therapy decreased tolerability compared with monotherapy and resulted in greater weight gain. There were not sufficient data to compare 1 co-therapy regimen with another. The meta-analysis concluded that addition of antipsychotic treatment to established mood stabilizer treatment is more effective than treatment with mood stabilizer alone.

A 2003 Cochrane review reported that oral olanzapine, lithium, and valproate are relatively equal in terms of effectiveness for the treatment of acute mania; however, lithium and valproate may take days to weeks for the patient to experience a full therapeutic response.[629] Acutely manic patients may require an antipsychotic drug or temporary treatment with a benzodiazepine.

Schizophrenia

A network meta-analysis compared the efficacy and safety of aripiprazole lauroxil (AL) and paliperidone palmitate (PP) (3 studies with PP, 1 with AL) in patients with schizophrenia.[630] All 4 active-treatment conditions (2 doses of each product: 441 mg or 882 mg once monthly of AL, 156 mg or 234 mg once monthly of PP) demonstrated comparable reductions in acute symptoms as measured by the PANSS versus placebo. The incidence of selected safety or tolerability parameters between agents was similar.

A meta-analysis evaluated the impact of long-acting injectable antipsychotic frequency (every 2 or 4 weeks) on efficacy and other outcomes, such as compliance (7 studies; n=3,994).[631] Antipsychotics included in the analysis included olanzapine, paliperidone, risperidone, haloperidol, and fluphenazine and included follow-up of up to 1 year. No differences were found in psychotic symptoms or quality of

life between injectables dosed every 2 or 4 weeks. Safety analyses were also very similar, with the exception of injection-site pain, which was lower with every 2 week formulations compared to every 4 week formulations (relative risk [RR], 0.16; 95% CI, 0.07 to 0.38; 2 studies; n=1,667). Overall, data were very limited.

A Cochrane meta-analysis examined if treatment with antipsychotic combinations is safe and effective for schizophrenia (62 studies).[632] Notably, half of the included studies compared clozapine monotherapy to combination therapy including clozapine and study risk was considered to be moderate to high. Based on this limited evidence, combination therapy was found to be superior to monotherapy in improving clinical response (RR, 0.73 [95% CI, 0.63 to 0.85]; n=2,364 [29 studies]), however, the authors conceded that much of this was due to the clozapine-containing studies which reported a RR of 0.66 (95% CI, 0.53 to 0.83; n=1,127 [17 studies]). In addition, the authors did not find a statistically significant improvement in relapse prevention (RR, 0.63 [95% CI, 0.31 to 1.29]; n=512 [3 studies]), reduction in those discontinuing treatment early (RR, 0.89 [95% CI, 0.73 to 1.07]; n=3,103 [43 studies]), or hospitalizations (RR, 0.96 [95% CI, 0.36 to 2.55]; n=202 [3 studies]). Nonetheless, no difference was found in serious adverse events (RR, 1.05 [95% CI, 0.65 to 1.69]; n=2,398 [30 studies]).

Tourette's Disorder

A meta-analysis of trials evaluating the efficacy of aripiprazole for children (ages 4 to 18 years) with tic disorders, such as Tourette's disorder (12 studies of 8 to 12 weeks in duration; n=935).[633] Trials included those with placebo- or active-controls. Overall, no significant difference was found in total YGTSS score reduction between aripiprazole and other active-controls (p=0.87; 7 studies; n=600), 4 of which were trials comparing aripiprazole and haloperidol. Other active controls included risperidone (not approved for this indication) and tiapride (not available in the US).

SUMMARY

There is inconclusive evidence whether overall effectiveness of second generation antipsychotics is better than that for first generation agents in terms of meeting primary outcomes of changes in rating scale scores, particularly considering the length of these studies, which is rarely beyond 12 weeks. Second generation antipsychotics are associated with less extrapyramidal symptoms (EPS) than first generation antipsychotics. The question of long-term adverse events with second generation antipsychotic use remains unresolved, particularly related to metabolic disorders. Second generation antipsychotics have largely replaced first generation antipsychotics in the treatment of psychotic disorders, but the long-term effectiveness and adverse event profiles of these products have not been shown to be definitively better.

Currently, inconclusive data exist concerning which second generation antipsychotic agent to use first, but various guidelines exist to help guide the clinician in choosing the best individualized treatment for schizophrenia, bipolar disorder, or major depressive disorder. Relative occurrences of adverse events can be used to guide product selection: weight gain, glucose abnormalities, lipid abnormalities, and diabetes occur more frequently with clozapine (Clozaril, Fazaclo, Versacloz) and olanzapine (Zyprexa, Zyprexa Relprevv). Clozapine has also been associated with significant orthostatic hypotension leading to rare collapse and respiratory/cardiac arrest and rare fatal myocarditis. Risperidone (Perseris, Risperdal, Risperdal Consta) and paliperidone (Invega, Invega Sustenna, Invega Trinza) have been associated with prolactin elevation more frequently than other second generation antipsychotics. Asenapine (Saphris), clozapine (Clozaril, Fazaclo, Versacloz),

iloperidone (Fanapt), paliperidone ER (Invega, Invega Sustenna, Invega Trinza), pimavanserin (Nuplazid), and ziprasidone (Geodon) have a warning of QT prolongation and risk of sudden death due to cardiac conduction abnormalities, and this is also a notable adverse effect of some first-generation antipsychotics (e.g., pimozide, haloperidol). Paliperidone ER (Invega) has a warning against its use in patients with gastrointestinal strictures due to reports of obstructions. Aripiprazole (Abilify), brexpiprazole (Rexulti), quetiapine (Seroquel, Seroquel XR), and olanzapine/fluoxetine (Symbyax) have a boxed warning concerning an increased risk of suicidality in children, adolescents, and young adults with major depressive disorders. All antipsychotics have a boxed warning regarding an increased incidence of mortality when these agents are used in elderly patients with dementia-related psychosis. Drug interactions should also be considered, particularly as many of these agents are substrates of CYP3A4 and/or CYP2D6.

The only inhaled antipsychotic available, loxapine inhalation powder (Adasuve), is approved for acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. It carries clinical restrictions including a boxed warning regarding bronchospasm that can potentially lead to respiratory distress or arrest.

Clozapine is used for patients with treatment-resistant schizophrenia and in patients with recurrent suicidal behavior at high risk of suicide. Clozapine is reserved for refractory patients due to rare reports of severe neutropenia and seizures occurring, among other serious adverse events, and patients taking it must have regular white blood cell and absolute neutrophil counts closely monitored.

There are not enough comparative data to support distinctions among the injectable second generation antipsychotics. Long-acting injectable risperidone (Risperdal Consta) and aripiprazole (Abilify Maintena) are the only intramuscular products approved for maintenance therapy of bipolar disorder. Risperidone for SC administration (Perseris) was recently approved for treatment of schizophrenia in adults. Unlike IM risperidone (Risperdal Consta), it does not generally require supplementation with oral risperidone during the first 3 weeks of injectable therapy.

Aripiprazole (Abilify Mycite) is a drug-device combination product of aripiprazole tablets embedded with an ingestible event marker (IEM) sensor intended to track drug ingestion. It is approved for use in adults only. Its ability to improve patient compliance or modify dosage has not been established. Likewise, it should not be used in “real-time” or emergency situations to track ingestion as detection may not occur or may be delayed. Its role in therapy has yet to be established.

Pimavanserin is the first drug approved for the treatment of psychosis associated with Parkinson’s disease. It is a selective serotonin inverse agonist (SSIA), targeting 5-HT_{2A} receptors and, to a lesser extent, 5-HT_{2C} receptors. Pimavanserin does not impair motor function in patients with PD psychosis. Its use has not been addressed in clinical practice guidelines due to its recent approval. Guidelines from the American Academy of Neurology (AAN) do suggest a role for other antipsychotics (e.g., clozapine, quetiapine) in this indication, but their use for this purpose is not FDA-approved.

REFERENCES

1 Perphenazine/amitriptyline [package insert]. Morgantown, WV; Mylan; November 2016.
2 Chlorpromazine HCl tablets [package insert]. Minneapolis, MN; Upsher-Smith; August 2017.
3 Fluphenazine HCl tablets [package insert]. Morgantown, WV; Mylan; November 2016.
4 Haloperidol tablets. Available at: https://www.micromedexsolutions.com. Accessed April 26, 2019.
5 Loxapine capsules [package insert]. Morgantown, WV; Mylan; March 2017.
6 Molindone HCl [package insert]. Laurelton, NY; Epic; April 2018.
7 Perphenazine [package insert]. Princeton, NJ; Sandoz; January 2018.
8 Orap [package insert]. Horsham, PA; Teva; August 2018.
9 Thioridazine [package insert]. Morgantown, WV; Mylan; November 2016.
10 Clinical Pharmacology. Available at: http://www.clinicalpharmacology.com/. Accessed April 26, 2019.
11 Thiothixene [package insert]. Morgantown, WV; Mylan; January 2010.
12 Clinical Pharmacology. Available at: http://www.clinicalpharmacology.com/. Accessed April 26, 2019.
13 Adasuve [package insert]. Mountain View, CA; Alexza; August 2017.
14 Chlorpromazine HCl injection [package insert]. Eatontown, NJ; Westward; November 2016.
15 Fluphenazine HCl injection [package insert]. Lake Zurich, IL; Fresenius Kabi; November 2016.
16 Haldol injection [package insert]. Titusville, NJ, Janssen; March 2019.
17 Fluphenazine decanoate [package insert]. Eatontown, NJ; Westward; November 2016.
18 Haldol Decanoate [package insert]. Titusville, NJ; Janssen; March 2019.
19 Abilify [package insert]. Rockville, MD; Otsuka; February 2018.
20 Abilify Mycite [package insert]. Rockville, MD; Otsuka; November 2017.
21 Saphris [package insert. Irvine, CA; Allergan; February 2017.
22 Rexulti [package insert]. Rockville, MD; Otsuka; February 2018.
23 Vraylar [package insert]. Irvine, CA; Allergan; November 2018.
24 Clozaril [package insert]. Rosemont, PA; February 2017.
25 Fazaclo [package insert]. Palo Alto, CA; Jazz; February 2017.
26 Versacloz [package insert]. Palo Alto, CA; Jazz; January 2018.
27 Fanapt [package insert]. Washington, DC; Vanda; February 2017.
28 Latuda [package insert]. Marlborough, MA; Sunovion; March 2018.
29 Zyprexa [package insert]. Indianapolis, IN; Lilly; March 2018.
30 Symbyax [package insert]. Indianapolis, IN; Lilly; March 2018.
31 Invega [package insert]. Titusville, NJ; Janssen; January 2019.
32 Nuplazid [package insert]. San Diego, CA; Acadia; March 2019.
33 Seroquel [package insert]. Wilmington, DE; AstraZeneca; November 2018.
34 Seroquel XR [package insert]. Wilmington, DE; AstraZeneca; November 2018.
35 Risperdal [package insert]. Titusville, NJ; Janssen; January 2019.
36 Geodon [package insert]. Morris Plains, NJ; Pfizer; November 2018.
37 Zyprexa [package insert]. Indianapolis, IN; Lilly; March 2018.
38 Geodon [package insert]. Morris Plains, NJ; Pfizer; November 2018.
39 Abilify Maintena [package insert]. Rockville, MD; Otsuka; March 2018.
40 Aristada [package insert]. Waltham, MA; Alkermes; November 2018.
41 Aristada Initio [package insert]. Waltham, MA; Alkermes; June 2018.
42 Zyprexa Relprevv [package insert]. Indianapolis, IN; Lilly; March 2018.
43 Invega Sustenna [package insert]. Titusville, NJ; Janssen; January 2019
44 Invega Trinza [package insert]. Titusville, NJ; Janssen; January 2019.
45 Risperdal Consta [package insert]. Titusville, NJ; Janssen; January 2019.
46 Perseris [package insert]. North Chesterfield, PA; Indivior; July 2018.
47 Perseris FDA Approval letter. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/210655Orig1s000ltr.pdf. Accessed April 26, 2019.
48 Available at: https://www.fda.gov/downloads/Drugs/Guidances/ucm079345.pdf. Accessed April 26, 2019.
49 Mueser KT, McGurk SR. Schizophrenia. Lancet. 2004; 363: 2063-2072.
50 Tandon R, Gaebel, W, Barch, D, et al. Definition and description of schizophrenia in the DSM-5, Schizophr Res. 2013; 150(1): 3-10. DOI: 10.1016/j.schres.2013.05.028.
51 American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia. 2nd ed. Arlington, VA: American Psychiatric Association; 2004; 114. Available at: https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines. Accessed April 26, 2019.
52 American Psychiatric Association. Guideline Watch (September 2009): Practice guideline for the treatment of patients with schizophrenia. Available at: https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines. Accessed April 26, 2019.
53 McClellan J, Stock S for the American Academy of Child and Adolescent Psychiatry Committee on Quality Issues. Practice Parameter for the assessment and treatment of children and adolescents with schizophrenia. J Am Acad Child Adolesc Psychiatry. 2013; 52(9): 976-990. DOI: 10.1016/j.jaac.2013.02.008. Available at: https://www.aacap.org/aacap/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx. Accessed April 26, 2019.
54 Bipolar Affective Disorder. Updated May 6, 2018. Available at: http://emedicine.medscape.com/article/286342-overview#a5. Accessed April 26, 2019.

55 DSM-5. Highlights of Changes from DSM-IV-TR to DSM-5. Available at: http://dsm.psychiatryonline.org/doi/abs/10.1176/appi.books.9780890425596.changes. Accessed April 26, 2019.
56 American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder. Am J Psychiatry. 2002; 159 (suppl 4): 1-50. Available at: Available at: http://psychiatryonline.org/guidelines. Accessed April 26, 2019.
57 American Psychiatric Association. Guideline Watch: Practice guideline for the treatment of patients with bipolar disorder. Available at: http://psychiatryonline.org/guidelines. Accessed April 26, 2019.
58 American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder. Am J Psychiatry. 2002; 159 (suppl 4): 1-50. Available at: Available at: http://psychiatryonline.org/guidelines. Accessed December 3, 2018.
59 American Psychiatric Association. Guideline Watch: Practice guideline for the treatment of patients with bipolar disorder. Available at: http://psychiatryonline.org/guidelines. Accessed April 26, 2019.
60 American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder. Am J Psychiatry. 2002; 159 (suppl 4): 1-50.
61 American Psychiatric Association. Guideline Watch: Practice guideline for the treatment of patients with bipolar disorder. Available at: http://psychiatryonline.org/guidelines. Accessed April 26, 2019.
62 Schizoaffective Disorder. Available at: http://www.nami.org/Learn-More/Mental-Health-Conditions/Schizoaffective-Disorder. Accessed April 26, 2019.
63 National Institute of Mental Health (US). Available at: https://www.nimh.nih.gov/health/statistics/major-depression.shtml. Accessed April 26, 2019.
64 US Preventive Services Task Force. Screening for depression in children and adolescents: US Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2016; 164(5): 360-366. DOI: 10.7326/M15-2957.
65 US Preventive Services Task Force. Screening for depression in adults: US Preventive Services Task Force Recommendation Statement. JAMA. 2016; 315(4): 380-387. DOI: 10.1001/jama.2015.18392. Available at: https://www.uspreventiveservicestaskforce.org/BrowseRec/Search?s=depression. Accessed April 26, 2019.
66 American Psychiatric Association. Practice guideline for the treatment of patients with Major Depressive Disorder. Third Edition. 2010. Available at: http://psychiatryonline.org/guidelines. Accessed April 26, 2019.
67 Qaseem A, Barry MJ, Kansagara D, et al for the Clinical Guidelines Committee of the American College of Physicians. Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2016; 164(5): 350-359. DOI: 10.7326/M15-2570, Available at: https://www.acponline.org/clinical-information/guidelines. Accessed April 26, 2019.
68 Autism. Last updated November 27, 2018. Available at: http://emedicine.medscape.com/article/912781-overview#a5. Accessed April 26, 2019.
69 Drugs@FDA. Available at: http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed April 26, 2019.
70 Volkmar F, Siegel M, Woodbury-Smith M, et al. Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. 2014; 53(2): 237-257. DOI: 10.1016/j.jaac.2013.10.013. Available at: https://www.aacap.org/aacap/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx. Accessed April 26, 2019.
71 McGuire K, Fung LK, Hagopian L, et al. Irritability and problem behavior in autism spectrum disorder: a practice pathway in pediatric primary care. Pediatrics. 2016; 137(Suppl 2): S136-S148). DOI: 10.1542/peds.2015-2851L. Available at: http://pediatrics.aappublications.org/content/137/Supplement_2/S136.long. Accessed April 26, 2019.
72 American Academy of Neurology. Practice Guideline: The Treatment of Tics in People with Tourette Syndrome and Chronic Tic Disorders. Available at: https://www.aan.com/Guidelines/home/GuidelineDetail/958. Accessed May 20, 2019.
73 Tourette Syndrome and Other Tic Disorders. Last updated January 11, 2017. Available at: http://emedicine.medscape.com/article/1182258-overview#a1. Accessed April 26, 2019.December 3, 2018.
74 American Academy of Neurology. Practice Guideline: The Treatment of Tics in People with Tourette Syndrome and Chronic Tic Disorders. Available at: https://www.aan.com/Guidelines/home/GuidelineDetail/958. Accessed May 20, 2019.
75 American Academy of Neurology. Practice Guideline: The Treatment of Tics in People with Tourette Syndrome and Chronic Tic Disorders. Available at: https://www.aan.com/Guidelines/home/GuidelineDetail/958. Accessed May 20, 2019.
76 Murphy TK, Lewin AB, Storch EA, et al. Practice parameter for the assessment and treatment of children and adolescents with tic disorders. J Am Acad Child Adolesc Psychiatry. 2013; 52(12): 1341-1359. DOI: 10.1016/j.jaac.2013.09.015. Available at: https://www.aacap.org/aacap/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx. Accessed April 26, 2019.
77 Drugs@FDA. Available at: http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed April 26, 2019.
78 National Parkinson Foundation. Available at: http://parkinson.org/sites/default/files/Parkinsons%20Disease%20Fact%20Sheet.pdf. Accessed April 26, 2019.
79 Paha R, Factor SA, Lyons KE, et al. Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review). Neurology. 2006; 66:983-95.
80 Beers MH, Berkos R, eds. The Merck Manual of Geriatrics. 3rd ed. Whitehouse Station, NJ: Merck & Co; 2000:432-41.
81 National Parkinson Foundation. Available at: http://parkinson.org/Understanding-Parkinsons/Symptoms/Non-Movement-Symptoms/Hallucinations-Delusions. Accessed April 26, 2019.
82 American Academy of Neurology Evaluation and Treatment of Depression, Psychosis, and Dementia in Parkinson Disease. Available at: http://tools.aan.com/professionals/practice/guidelines/Eval_Treatment_PD_Sum.pdf. Accessed April 26, 2019.
83 Drugs@FDA. Available at: http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed April 26, 2019.
84 Reus VI, Fochtmann LJ, Eyler EA, et al. The American Psychiatric Association practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia. American Psychiatric Association. Am J Psychiatry. 2016; 173(5): 543-546. DOI: 10.1176/appi.ajp.2015.173501. Available at: https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines. Accessed April 26, 2019.
85 Seppi K, Ray Chaudhuri K, Coelho M, et al for the collaborators of the Parkinson's Disease Update on Non-Motor Symptoms Study Group on behalf of the Movement Disorders Society Evidence-Based Medicine Committee. Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review. Mov Disord. 2019;34(2):180-198. DOI: 10.1002/mds.27602.
86 Perphenazine/amitriptyline [package insert]. Morgantown, WV; Mylan; November 2016.
87 Chlorpromazine HCl tablets [package insert]. Minneapolis, MN; Upsher-Smith; August 2017.
88 Fluphenazine HCl tablets [package insert]. Morgantown, WV; Mylan; November 2016.

89 Haloperidol tablets [package insert]. Morgantown, WV; Mylan; November 2016.
90 Loxapine capsules [package insert]. Morgantown, WV; Mylan; March 2017.
91 Molindone HCl [package insert]. Laurelton, NY; Epic; April 2018.
92 Perphenazine [package insert]. Princeton, NJ; Sandoz; January 2018.
93 Orap [package insert]. Horsham, PA; Teva; August 2018.
94 Thioridazine [package insert]. Morgantown, WV. Mylan; November 2016.
95 Clinical Pharmacology. Available at: http://www.clinicalpharmacology.com/. Accessed April 26, 2019.
96 Thiothixene [package insert]. Morgantown, WV; Mylan; January 2010.
97 Adasuve [package insert]. Mountain View, CA; Alexza; August 2017.
98 Chlorpromazine HCl injection [package insert]. Eatontown, NJ; Westward; November 2016.
99 Fluphenazine decanoate [package insert]. Eatontown, NJ; Westward; November 2016.
100 Fluphenazine HCl injection [package insert]. Lake Zurich, IL; Fresenius Kabi; November 2016.
101 Haldol Decanoate [package insert]. Titusville, NJ; Janssen; March 2019.
102 Haldol injection [package insert]. Titusville, NJ, Janssen; March 2019.
103 Abilify [package insert]. Rockville, MD; Otsuka; February 2018.
104 Abilify Mycite [package insert]. Rockville, MD; Otsuka; November 2017.
105 Saphris [package insert]. Irvine, CA; Allergan; February 2017.
106 Rexulti [package insert]. Rockville, MD; Otsuka; February 2018.
107 Vraylar [package insert]. Irvine, CA; Allergan; November 2018.
108 Clozaril [package insert]. Rosemont, PA; February 2017.
109 Fazaclo [package insert]. Palo Alto, CA; Jazz; February 2017.
110 Versacloz [package insert]. Palo Alto, CA; Jazz; January 2018.
111 Fanapt [package insert]. Washington, DC; Vanda; February 2017.
112 Latuda [package insert]. Marlborough, MA; Sunovion; March 2018.
113 Zyprexa [package insert]. Indianapolis, IN; Lilly; March 2018.
114 Symbyax [package insert]. Indianapolis, IN; Lilly; March 2018.
115 Invega [package insert]. Titusville, NJ; Janssen; January 2019.
116 Seroquel [package insert]. Wilmington, DE; AstraZeneca; November 2018.
117 Seroquel XR [package insert]. Wilmington, DE; AstraZeneca; November 2018.
118 Risperdal [package insert]. Titusville, NJ; Janssen; January 2019.
119 Geodon [package insert]. Morris Plains, NJ; Pfizer; November 2018.
120 Abilify Maintena [package insert]. Rockville, MD; Otsuka; March 2018.
121 Aristada [package insert]. Waltham, MA; Alkermes; November 2018.
122 Zyprexa Relprevv [package insert]. Indianapolis, IN; Lilly; March 2018.
123 Invega Sustenna [package insert]. Titusville, NJ; Janssen; January 2019.
124 Invega Trinza [package insert]. Titusville, NJ; Janssen; January 2019.
125 Perseris [package insert]. North Chesterfield, PA; Indivior; July 2018.
126 Risperdal Consta [package insert]. Titusville, NJ; Janssen; January 2019.
127 Geodon [package insert]. Morris Plains, NJ; Pfizer; November 2018.
128 Nuplazid [package insert]. San Diego, CA; Acadia; March 2019.
129 Schotte A, Janssen PF, Gommeren W, et al. Risperidone compared with new and reference antipsychotic drugs: in vitro and in vivo receptor binding. Psychopharmacol. 1996; 124:57–73.
130 Richelson E, Souder T. Binding of antipsychotic drugs to human brain receptors focus on newer generation compounds. Life Sci. 2000; 68:29–39.
131 Kroeze WK, Hufeisen SJ, Popadak BA, et al. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. Neuropsychopharmacol. 2003; 28:519–26.
132 Zeng XP, Le F, Richelson E. Muscarinic m4 receptor activation by some atypical antipsychotic drugs. Eur J Pharmacol. 1997; 321: 349–54.
133 Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry. 2004; 161(2 Suppl): 1-56.
134 Nemeroff CB, Kinkead B, Goldstein J. Quetiapine: preclinical studies, pharmacokinetics, drug interactions, and dosing. J Clin Psychiatry. 2002; 63(suppl 13): 5–11.
135 Schmidt AW, Lebel LA, Howard HR Jr, et al. Ziprasidone: a novel antipsychotic agent with a unique human receptor binding profile. Eur J Pharmacol. 2001; 425: 197–201.
136 Burris KD, Molski TF, Xu C, et al. Aripiprazole, a novel antipsychotic, is a high affinity partial agonist at human dopamine D2 receptors. J Pharmacol Exp Ther. 2002; 302: 381–389.
137 Shapiro DA, Renock S, Arrington E, et al. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. Neuropsychopharmacol. 2003; 28(8): 1400–1411.
138 Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry. 1988; 45: 789-796.
139 Worrel JA, Marken PA, Backman SE, et al. Atypical antipsychotic agents: A critical review. Am J Health-Syst Pharm. 2000; 57: 238-258.
140 Kapur S, Seeman P. Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics?: a new hypothesis. Am J Psychiatry. 2001; 158: 360-369.
141 Stahl SM. "Hit-and-run" actions at dopamine receptors, part 1: mechanism of action of atypical antipsychotics. J Clin Psychiatry. 2001; 62: 670-671.
142 Aristada Initio [package insert]. Waltham, MA; Alkermes; June 2018.
143 Perphenazine/amitriptyline [package insert]. Morgantown, WV; Mylan; November 2016.
144 Chlorpromazine HCl tablets [package insert]. Minneapolis, MN; Upsher-Smith; August 2017.

145 Fluphenazine HCl tablets [package insert]. Morgantown, WV; Mylan; November 2016.
146 Haloperidol tablets [package insert]. Morgantown, WV; Mylan; November 2016.
147 Loxapine capsules [package insert]. Morgantown, WV; Mylan; March 2017.
148 Molindone HCl [package insert]. Laurelton, NY; Epic; April 2018.
149 Perphenazine [package insert]. Princeton, NJ; Sandoz; January 2018.
150 Orap [package insert]. Horsham, PA; Teva; August 2018.
151 Thioridazine [package insert]. Morgantown, WV. Mylan; November 2016.
152 Clinical Pharmacology. Available at: http://www.clinicalpharmacology.com/. Accessed December 3, 2018.
153 Thiothixene [package insert]. Morgantown, WV; Mylan; January 2010.
154 Adasuve [package insert]. Mountain View, CA; Alexza; August 2017.
155 Chlorpromazine HCl injection [package insert]. Eatontown, NJ; Westward; November 2016.
156 Fluphenazine decanoate [package insert]. Eatontown, NJ; Westward; November 2016.
157 Fluphenazine HCl injection [package insert]. Lake Zurich, IL; Fresenius Kabi; November 2016.
158 Haldol Decanoate [package insert]. Titusville, NJ; Janssen; March 2019.
159 Haldol injection [package insert]. Titusville, NJ, Janssen; March 2019.
160 Abilify [package insert]. Rockville, MD; Otsuka; February 2018.
161 Abilify Mycite [package insert]. Rockville, MD; Otsuka; November 2017.
162 Saphris [package insert]. Irvine, CA; Allergan; February 2017.
163 Rexulti [package insert]. Rockville, MD; Otsuka; February 2018.
164 Vraylar [package insert]. Irvine, CA; Allergan; November 2018.
165 Clozaril [package insert]. Rosemont, PA; February 2017.
166 Fazaclo [package insert]. Palo Alto, CA; Jazz; February 2017.
167 Versacloz [package insert]. Palo Alto, CA; Jazz; January 2018.
168 Fanapt [package insert]. Washington, DC; Vanda; February 2017.
169 Latuda [package insert]. Marlborough, MA; Sunovion; March 2018.
170 Zyprexa [package insert]. Indianapolis, IN; Lilly; March 2018.
171 Symbyax [package insert]. Indianapolis, IN; Lilly; March 2018.
172 Invega [package insert]. Titusville, NJ; Janssen; January 2019.
173 Seroquel [package insert]. Wilmington, DE; AstraZeneca; November 2018.
174 Seroquel XR [package insert]. Wilmington, DE; AstraZeneca; November 2018.
175 Risperdal [package insert]. Titusville, NJ; Janssen; January 2019.
176 Geodon [package insert]. Morris Plains, NJ; Pfizer; November 2018.
177 Abilify Maintena [package insert]. Rockville, MD; Otsuka; March 2018.
178 Aristada [package insert]. Waltham, MA; Alkermes; November 2018.
179 Zyprexa Relprevv [package insert]. Indianapolis, IN; Lilly; March 2018.
180 Invega Sustenna [package insert]. Titusville, NJ; Janssen; January 2019.
181 Invega Trinza [package insert]. Titusville, NJ; Janssen; January 2019.
182 Perseris [package insert]. North Chesterfield, PA; Indivior; July 2018.
183 Risperdal Consta [package insert]. Titusville, NJ; Janssen; January 2019.
184 Geodon [package insert]. Morris Plains, NJ; Pfizer; November 2018.
185 Nuplazid [package insert]. San Diego, CA; Acadia; March 2019.
186 Cleton A, Talluri K, Leempoels J, et al. No pharmacokinetic interaction between trimethoprim and paliperidone ER in healthy subjects. Clin Pharmacol Ther. 2006; 79: 22.
187 Cleton A, Rossenu S, Vermeulen A, et al. A pharmacokinetic model to document the interconversion between paliperidone's enantiomers. Clin Pharmacol Ther. 2006; 79: 55.
188 Aristada Initio [package insert]. Waltham, MA; Alkermes; June 2018.
189 Perphenazine/amitriptyline [package insert]. Morgantown, WV; Mylan; November 2016.
190 Chlorpromazine HCl tablets [package insert]. Minneapolis, MN; Upsher-Smith; August 2017.
191 Fluphenazine HCl tablets [package insert]. Morgantown, WV; Mylan; November 2016.
192 Haloperidol tablets [package insert]. Morgantown, WV; Mylan; November 2016.
193 Loxapine capsules [package insert]. Morgantown, WV; Mylan; March 2017.
194 Molindone HCl [package insert]. Laurelton, NY; Epic; April 2018.
195 Perphenazine [package insert]. Princeton, NJ; Sandoz; January 2018.
196 Orap [package insert]. Horsham, PA; Teva; August 2018.
197 Thioridazine [package insert]. Morgantown, WV. Mylan; November 2016.
198 Clinical Pharmacology. Available at: http://www.clinicalpharmacology.com/. Accessed April 26, 2019.
199 Thiothixene [package insert]. Morgantown, WV; Mylan; January 2010.
200 Adasuve [package insert]. Mountain View, CA; Alexza; August 2017.
201 Chlorpromazine HCl injection [package insert]. Eatontown, NJ; Westward; November 2016.
202 Fluphenazine decanoate [package insert]. Eatontown, NJ; Westward; November 2016.
203 Fluphenazine HCl injection [package insert]. Lake Zurich, IL; Fresenius Kabi; November 2016.
204 Haldol Decanoate [package insert]. Titusville, NJ; Janssen; March 2019.
205 Haldol injection [package insert]. Titusville, NJ, Janssen; March 2019.
206 Abilify [package insert]. Rockville, MD; Otsuka; February 2018.
207 Abilify Mycite [package insert]. Rockville, MD; Otsuka; November 2017.

208 Saphris [package insert]. Irvine, CA; Allergan; February 2017.
209 Rexulti [package insert]. Rockville, MD; Otsuka; February 2018.
210 Vraylar [package insert]. Irvine, CA; Allergan; November 2018.
211 Clozaril [package insert]. Rosemont, PA; February 2017.
212 Fazaclo [package insert]. Palo Alto, CA; Jazz; February 2017.
213 Versacloz [package insert]. Palo Alto, CA; Jazz; January 2018.
214 Fanapt [package insert]. Washington, DC; Vanda; February 2017.
215 Latuda [package insert]. Marlborough, MA; Sunovion; March 2018.
216 Zyprexa [package insert]. Indianapolis, IN; Lilly; March 2018.
217 Symbyax [package insert]. Indianapolis, IN; Lilly; March 2018.
218 Invega [package insert]. Titusville, NJ; Janssen; January 2019.
219 Seroquel [package insert]. Wilmington, DE; AstraZeneca; November 2018.
220 Seroquel XR [package insert]. Wilmington, DE; AstraZeneca; November 2018.
221 Risperdal [package insert]. Titusville, NJ; Janssen; January 2019.
222 Geodon [package insert]. Morris Plains, NJ; Pfizer; November 2018.
223 Abilify Maintena [package insert]. Rockville, MD; Otsuka; March 2018.
224 Aristada [package insert]. Waltham, MA; Alkermes; November 2018.
225 Zyprexa Relprevv [package insert]. Indianapolis, IN; Lilly; March 2018.
226 Invega Sustenna [package insert]. Titusville, NJ; Janssen; January 2019.
227 Invega Trinza [package insert]. Titusville, NJ; Janssen; January 2019.
228 Perseris [package insert]. North Chesterfield, PA; Indivior; July 2018.
229 Risperdal Consta [package insert]. Titusville, NJ; Janssen; January 2019.
230 Geodon [package insert]. Morris Plains, NJ; Pfizer; November 2018.
231 Nuplazid [package insert]. San Diego, CA; Acadia; March 2019.
232 Aristada Initio [package insert]. Waltham, MA; Alkermes; June 2018.
233 Available at: https://psychnews.psychiatryonline.org/doi/10.1176/pn.43.14.0001. Accessed April 26, 2019.
234 American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia. 2nd ed. Arlington, VA: American Psychiatric Association; 2004; 114.
235 Ray WA, Chung CP, Murray KT, et al. Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med. 2009; 360(3):225-235.
236 Available at: https://www.fda.gov/Drugs/DrugSafety/ucm498662.htm. Accessed April 26, 2019.
237 Available at: https://www.fda.gov/Drugs/DrugSafety/ucm499441.htm. Accessed April 26, 2019.
238 Available at: http://ir.acadia-pharm.com/phoenix.zhtml?c=125180&p=irol-newsArticle&ID=2345257. Accessed April 26, 2019.
239 Available at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070093.htm. Accessed April 26, 2019.
240 Available at: https://www.fda.gov/Drugs/DrugSafety/ucm621160.htm. Accessed April 26, 2019.
241 REMS@FDA. Available at: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm. Accessed April 24, 2019.
242 Clozapine: Shared REMS. Available at: http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=351. Accessed April 26, 2019.
243 Perphenazine/amitriptyline [package insert]. Morgantown, WV; Mylan; November 2016.
244 Chlorpromazine HCl tablets [package insert]. Minneapolis, MN; Upsher-Smith; August 2017.
245 Fluphenazine HCl tablets [package insert]. Morgantown, WV; Mylan; November 2016.
246 Haloperidol tablets [package insert]. Morgantown, WV; Mylan; November 2016.
247 Loxapine capsules [package insert]. Morgantown, WV; Mylan; March 2017.
248 Molindone HCl [package insert]. Laurelton, NY; Epic; April 2018.
249 Perphenazine [package insert]. Princeton, NJ; Sandoz; January 2018.
250 Orap [package insert]. Horsham, PA; Teva; August 2018.
251 Thioridazine [package insert]. Morgantown, WV. Mylan; November 2016.
252 Clinical Pharmacology. Available at: http://www.clinicalpharmacology.com/. Accessed April 26, 2019.
253 Thiothixene [package insert]. Morgantown, WV; Mylan; January 2010.
254 Adasuve [package insert]. Mountain View, CA; Alexza; August 2017.
255 Chlorpromazine HCl injection [package insert]. Eatontown, NJ; Westward; November 2016.
256 Fluphenazine decanoate [package insert]. Eatontown, NJ; Westward; November 2016.
257 Fluphenazine HCl injection [package insert]. Lake Zurich, IL; Fresenius Kabi; November 2016.
258 Haldol Decanoate [package insert]. Titusville, NJ; Janssen; March 2019.
259 Haldol injection [package insert]. Titusville, NJ, Janssen; March 2019.
260 Abilify [package insert]. Rockville, MD; Otsuka; February 2018.
261 Abilify Mycite [package insert]. Rockville, MD; Otsuka; November 2017.
262 Saphris [package insert]. Irvine, CA; Allergan; February 2017.
263 Rexulti [package insert]. Rockville, MD; Otsuka; February 2018.
264 Vraylar [package insert]. Irvine, CA; Allergan; November 2018.
265 Clozaril [package insert]. Rosemont, PA; February 2017.
266 Fazaclo [package insert]. Palo Alto, CA; Jazz; February 2017.
267 Versacloz [package insert]. Palo Alto, CA; Jazz; January 2018.
268 Fanapt [package insert]. Washington, DC; Vanda; February 2017.
269 Latuda [package insert]. Marlborough, MA; Sunovion; March 2018.

270 Zyprexa [package insert]. Indianapolis, IN; Lilly; March 2018.
271 Symbyax [package insert]. Indianapolis, IN; Lilly; March 2018.
272 Invega [package insert]. Titusville, NJ; Janssen; January 2019.
273 Seroquel [package insert]. Wilmington, DE; AstraZeneca; November 2018.
274 Seroquel XR [package insert]. Wilmington, DE; AstraZeneca; November 2018.
275 Risperdal [package insert]. Titusville, NJ; Janssen; January 2019.
276 Geodon [package insert]. Morris Plains, NJ; Pfizer; November 2018.
277 Abilify Maintena [package insert]. Rockville, MD; Otsuka; March 2018.
278 Aristada [package insert]. Waltham, MA; Alkermes; November 2018.
279 Zyprexa Relprevv [package insert]. Indianapolis, IN; Lilly; March 2018.
280 Invega Sustenna [package insert]. Titusville, NJ; Janssen; January 2019.
281 Invega Trinza [package insert]. Titusville, NJ; Janssen; January 2019.
282 Perseris [package insert]. North Chesterfield, PA; Indivior; July 2018.
283 Risperdal Consta [package insert]. Titusville, NJ; Janssen; January 2019.
284 Geodon [package insert]. Morris Plains, NJ; Pfizer; November 2018.
285 Nuplazid [package insert]. San Diego, CA; Acadia; March 2019.
286 Nuplazid [package insert]. San Diego, CA; Acadia; March 2019.
287 Saito M, Yasui-Furukoki N, Nakagami T, et al. Dose-dependent interaction of paroxetine with risperidone in schizophrenic patients. J Clin Psychopharmacol. 2005; 25: 527-532.
288 Jung SM, Kim KA, Cho HK, et al. Cytochrome P450 3A inhibitor itraconazole affects plasma concentrations of risperidone and 9-hydroxyrisperidone in schizophrenic patients. Clin Pharmacol Ther. 2005; 78: 520-528.
289 Aristada Initio [package insert]. Waltham, MA; Alkermes; June 2018.
290 Perphenazine/amitriptyline [package insert]. Morgantown, WV; Mylan; November 2016.
291 Chlorpromazine HCl tablets [package insert]. Minneapolis, MN; Upsher-Smith; August 2017.
292 Fluphenazine HCl tablets [package insert]. Morgantown, WV; Mylan; November 2016.
293 Haloperidol tablets [package insert]. Morgantown, WV; Mylan; November 2016.
294 Loxapine capsules [package insert]. Morgantown, WV; Mylan; March 2017.
295 Molindone HCl [package insert]. Laurelton, NY; Epic; April 2018.
296 Perphenazine [package insert]. Princeton, NJ; Sandoz; January 2018.
297 Orap [package insert]. Horsham, PA; Teva; August 2018.
298 Thioridazine [package insert]. Morgantown, WV. Mylan; November 2016.
299 Clinical Pharmacology. Available at: http://www.clinicalpharmacology.com/. Accessed April 26, 2019.
300 Thiothixene [package insert]. Morgantown, WV; Mylan; January 2010.
301 Adasuve [package insert]. Mountain View, CA; Alexza; August 2017.
302 Chlorpromazine HCl injection [package insert]. Eatontown, NJ; Westward; November 2016.
303 Fluphenazine decanoate [package insert]. Eatontown, NJ; Westward; November 2016.
304 Fluphenazine HCl injection [package insert]. Lake Zurich, IL; Fresenius Kabi; November 2016.
305 Haldol Decanoate [package insert]. Titusville, NJ; Janssen; March 2019.
306 Haldol injection [package insert]. Titusville, NJ, Janssen; March 2019.
307 Abilify [package insert]. Rockville, MD; Otsuka; February 2018.
308 Abilify Mycite [package insert]. Rockville, MD; Otsuka; November 2017.
309 Saphris [package insert]. Irvine, CA; Allergan; February 2017.
310 Rexulti [package insert]. Rockville, MD; Otsuka; February 2018.
311 Vraylar [package insert]. Irvine, CA; Allergan; November 2018.
312 Clozaril [package insert]. Rosemont, PA; February 2017.
313 Fazaclo [package insert]. Palo Alto, CA; Jazz; February 2017.
314 Versacloz [package insert]. Palo Alto, CA; Jazz; January 2018.
315 Fanapt [package insert]. Washington, DC; Vanda; February 2017.
316 Latuda [package insert]. Marlborough, MA; Sunovion; March 2018.
317 Zyprexa [package insert]. Indianapolis, IN; Lilly; March 2018.
318 Symbyax [package insert]. Indianapolis, IN; Lilly; March 2018.
319 Invega [package insert]. Titusville, NJ; Janssen; January 2019.
320 Seroquel [package insert]. Wilmington, DE; AstraZeneca; November 2018.
321 Seroquel XR [package insert]. Wilmington, DE; AstraZeneca; November 2018.
322 Risperdal [package insert]. Titusville, NJ; Janssen; January 2019.
323 Geodon [package insert]. Morris Plains, NJ; Pfizer; November 2018.
324 Abilify Maintena [package insert]. Rockville, MD; Otsuka; March 2018.
325 Aristada [package insert]. Waltham, MA; Alkermes; November 2018.
326 Zyprexa Relprevv [package insert]. Indianapolis, IN; Lilly; March 2018.
327 Invega Sustenna [package insert]. Titusville, NJ; Janssen; January 2019.
328 Invega Trinza [package insert]. Titusville, NJ; Janssen; January 2019.
329 Perseris [package insert]. North Chesterfield, PA; Indivior; July 2018.
330 Risperdal Consta [package insert]. Titusville, NJ; Janssen; January 2019.
331 Geodon [package insert]. Morris Plains, NJ; Pfizer; November 2018.
332 Nuplazid [package insert]. San Diego, CA; Acadia; March 2019.

333 Aristada Initio [package insert]. Waltham, MA; Alkermes; June 2018.
334 Lamberti JS, Olson D, Crilly JF, et al. Prevalence of the metabolic syndrome among patients receiving clozapine. Am J Psychiatry. 2006; 163: 1723-1726.
335 Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry. 2004; 161(2 Suppl):1-56.
336 Kemp DE, Calabrese JR, Tran QV, et al. Metabolic syndrome in patients enrolled in a clinical trial of aripiprazole in the maintenance treatment of bipolar I disorder: a post hoc analysis of a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2010; 71(9): 1138-1144.
337 Ereshefsky L. Pharmacologic and pharmacokinetic considerations in choosing an antipsychotic. J Clin Psychiatry. 1999; 60: 21.
338 McIntyre RS, Mancini DA, Basile VS, et al. Antipsychotic-induced weight gain: bipolar disorder and leptin. J Clin Psychopharmacol. 2003; 23: 323-327.
339 Wirshing DA, Boyd JA, Meng LR, et al. The effects of novel antipsychotics on glucose and lipid levels. J Clin Psychiatry. 2002; 63: 856-865.
340 Leslie DL, Rosenheck RA. Incidence of newly diagnosed diabetes attributable to atypical antipsychotic medications. Am J Psychiatry. 2004; 161: 1709-1711.
341 Lamberti JS, Costea GO, Olson D, et al. Diabetes mellitus among outpatients receiving clozapine: prevalence and clinical-demographic correlates. J Clin Psychiatry. 2005; 66: 900-906.
342 Ostbye T, Curtis LH, Masselink LE, et al. Atypical antipsychotic drugs and diabetes mellitus in a large outpatient population: a retrospective cohort study. Pharmacoepidemiol Drug Saf. 2005; 14: 407-415.
343 Lambert BL, Cunningham FE, Miller DR, et al. Olanzapine, quetiapine, and risperidone in Veterans Health Administration Patients with schizophrenia. Am J Epidemiol. 2006; 164: 672-681.
344 Guo JJ, Keck PE Jr, Corey-Lisle PK, et al. Risk of diabetes mellitus associated with atypical antipsychotic use among patients with bipolar disorder: A retrospective, population-based, case-control study. J Clin Psychiatry. 2006; 67: 1055-1061.
345 Fedorowicz VJ, Fombonne E. Metabolic side effects of atypical antipsychotics in children: a literature review. J Psychopharmacol. 2005; 19: 533–550.
346 Safer DJ. A comparison of risperidone-induced weight gain across the age span. J Clin Psychopharmacol. 2004; 24: 429–436.
347 Klein DJ, Cottingham EM, Sorter M, et al. A randomized, double-blind, placebo-controlled trial of metformin treatment of weight gain associated with initiation of atypical antipsychotic therapy in children and adolescents. Am J Psychiatry. 2006; 163: 2072-2079.
348 Bobo WV, Cooper WO, Stein CM, et al. Antipsychotics and the risk of type 2 diabetes mellitus in children and youth. JAMA Psychiatry. 2013; 70(10): 1067-1075. DOI: 10.1001/jamapsychiatry.2013.2053.
349 Perphenazine/amitriptyline [package insert]. Morgantown, WV; Mylan; November 2016.
350 Chlorpromazine HCl tablets [package insert]. Minneapolis, MN; Upsher-Smith; August 2017.
351 Fluphenazine HCl tablets [package insert]. Morgantown, WV; Mylan; November 2016.
352 Haloperidol tablets [package insert]. Morgantown, WV; Mylan; November 2016.
353 Loxapine capsules [package insert]. Morgantown, WV; Mylan; March 2017.
354 Molindone HCl [package insert]. Laurelton, NY; Epic; April 2018.
355 Perphenazine [package insert]. Princeton, NJ; Sandoz; January 2018.
356 Orap [package insert]. Horsham, PA; Teva; August 2018.
357 Thioridazine [package insert]. Morgantown, WV. Mylan; November 2016.
358 Clinical Pharmacology. Available at: http://www.clinicalpharmacology.com/. Accessed April 26, 2019.
359 Thiothixene [package insert]. Morgantown, WV; Mylan; January 2010.
360 Adasuve [package insert]. Mountain View, CA; Alexza; August 2017.
361 Chlorpromazine HCl injection [package insert]. Eatontown, NJ; Westward; November 2016.
362 Fluphenazine decanoate [package insert]. Eatontown, NJ; Westward; November 2016.
363 Fluphenazine HCl injection [package insert]. Lake Zurich, IL; Fresenius Kabi; November 2016.
364 Haldol Decanoate [package insert]. Titusville, NJ; Janssen; March 2019.
365 Haldol injection [package insert]. Titusville, NJ, Janssen; March 2019.
366 Abilify [package insert]. Rockville, MD; Otsuka; February 2018.
367 Abilify Mycite [package insert]. Rockville, MD; Otsuka; November 2017.
368 Saphris [package insert]. Irvine, CA; Allergan; February 2017.
369 Rexulti [package insert]. Rockville, MD; Otsuka; February 2018.
370 Vraylar [package insert]. Irvine, CA; Allergan; November 2018.
371 Clozaril [package insert]. Rosemont, PA; February 2017.
372 Fazaclo [package insert]. Palo Alto, CA; Jazz; February 2017.
373 Versacloz [package insert]. Palo Alto, CA; Jazz; January 2018.
374 Fanapt [package insert]. Washington, DC; Vanda; February 2017.
375 Latuda [package insert]. Marlborough, MA; Sunovion; March 2018.
376 Zyprexa [package insert]. Indianapolis, IN; Lilly; March 2018.
377 Symbyax [package insert]. Indianapolis, IN; Lilly; March 2018.
378 Invega [package insert]. Titusville, NJ; Janssen; January 2019.
379 Seroquel [package insert]. Wilmington, DE; AstraZeneca; November 2018.
380 Seroquel XR [package insert]. Wilmington, DE; AstraZeneca; November 2018.
381 Risperdal [package insert]. Titusville, NJ; Janssen; January 2019.
382 Geodon [package insert]. Morris Plains, NJ; Pfizer; November 2018.
383 Abilify Maintena [package insert]. Rockville, MD; Otsuka; March 2018.
384 Aristada [package insert]. Waltham, MA; Alkermes; November 2018.
385 Zyprexa Relprevv [package insert]. Indianapolis, IN; Lilly; March 2018.
386 Invega Sustenna [package insert]. Titusville, NJ; Janssen; January 2019.
387 Invega Trinza [package insert]. Titusville, NJ; Janssen; January 2019.
388 Perseris [package insert]. North Chesterfield, PA; Indivior; July 2018.

389 Risperdal Consta [package insert]. Titusville, NJ; Janssen; January 2019.
390 Geodon [package insert]. Morris Plains, NJ; Pfizer; November 2018.
391 Nuplazid [package insert]. San Diego, CA; Acadia; March 2019.
392 Aristada Initio [package insert]. Waltham, MA; Alkermes; June 2018.
393 Available at: http://www.aacap.org/App_Themes/AACAP/docs/practice_parameters/Atypical_Antipsychotic_Medications_Web.pdf. Accessed April 26, 2019.
394 Available at: https://www.fda.gov/Drugs/DrugSafety/ucm243903.htm. Accessed April 26, 2019.
395 Ruxton K, Woodman RJ, Mangoni AA. Drugs with anticholinergic effects and cognitive impairment, falls and all-cause mortality in older adults: a systematic review and meta-analysis. Br J Clin Pharmacol. 2015; 80(2): 209-220. DOI: 10.1111/bcp.12617.
396 American Geriatrics Society 2019 Updated AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2019; 00:1-21. DOI: 10.1111/jgs.15767. Available at: https://nicheprogram.org/sites/niche/files/2019-02/Panel-2019-Journal_of_the_American_Geriatrics_Society.pdf/. Accessed May 20, 2019.
397 Available at: https://www.clozapinerems.com/CpmgClozapineUI/rems/pdf/resources/Clozapine_REMS_HCP_Guide.pdf. Accessed April 26, 2019.
398 Perphenazine/amitriptyline [package insert]. Morgantown, WV; Mylan; November 2016.
399 Chlorpromazine HCl tablets [package insert]. Minneapolis, MN; Upsher-Smith; August 2017.
400 Fluphenazine HCl tablets [package insert]. Morgantown, WV; Mylan; November 2016.
401 Haloperidol tablets [package insert]. Morgantown, WV; Mylan; November 2016.
402 Loxapine capsules [package insert]. Morgantown, WV; Mylan; March 2017.
403 Molindone HCl [package insert]. Laurelton, NY; Epic; April 2018.
404 Perphenazine [package insert]. Princeton, NJ; Sandoz; January 2018.
405 Orap [package insert]. Horsham, PA; Teva; August 2018.
406 Thioridazine [package insert]. Morgantown, WV. Mylan; November 2016.
407 Clinical Pharmacology. Available at: http://www.clinicalpharmacology.com/. Accessed April 26, 2019.
408 Thiothixene [package insert]. Morgantown, WV; Mylan; January 2010.
409 Adasuve [package insert]. Mountain View, CA; Alexza; August 2017.
410 Chlorpromazine HCl injection [package insert]. Eatontown, NJ; Westward; November 2016.
411 Fluphenazine decanoate [package insert]. Eatontown, NJ; Westward; November 2016.
412 Fluphenazine HCl injection [package insert]. Lake Zurich, IL; Fresenius Kabi; November 2016.
413 Haldol Decanoate [package insert]. Titusville, NJ; Janssen; March 2019.
414 Haldol injection [package insert]. Titusville, NJ, Janssen; March 2019.
415 Abilify [package insert]. Rockville, MD; Otsuka; February 2018.
416 Abilify Mycite [package insert]. Rockville, MD; Otsuka; November 2017.
417 Saphris [package insert]. Irvine, CA; Allergan; February 2017.
418 Rexulti [package insert]. Rockville, MD; Otsuka; February 2018.
419 Vraylar [package insert]. Irvine, CA; Allergan; November 2018.
420 Clozaril [package insert]. Rosemont, PA; February 2017.
421 Fazaclo [package insert]. Palo Alto, CA; Jazz; February 2017.
422 Versacloz [package insert]. Palo Alto, CA; Jazz; January 2018.
423 Fanapt [package insert]. Washington, DC; Vanda; February 2017.
424 Latuda [package insert]. Marlborough, MA; Sunovion; March 2018.
425 Zyprexa [package insert]. Indianapolis, IN; Lilly; March 2018.
426 Symbyax [package insert]. Indianapolis, IN; Lilly; March 2018.
427 Invega [package insert]. Titusville, NJ; Janssen; January 2019.
428 Seroquel [package insert]. Wilmington, DE; AstraZeneca; November 2018.
429 Seroquel XR [package insert]. Wilmington, DE; AstraZeneca; November 2018.
430 Risperdal [package insert]. Titusville, NJ; Janssen; January 2019.
431 Geodon [package insert]. Morris Plains, NJ; Pfizer; November 2018.
432 Abilify Maintena [package insert]. Rockville, MD; Otsuka; March 2018.
433 Aristada [package insert]. Waltham, MA; Alkermes; November 2018.
434 Zyprexa Relprevv [package insert]. Indianapolis, IN; Lilly; March 2018.
435 Invega Sustenna [package insert]. Titusville, NJ; Janssen; January 2019.
436 Invega Trinza [package insert]. Titusville, NJ; Janssen; January 2019.
437 Perseris [package insert]. North Chesterfield, PA; Indivior; July 2018.
438 Risperdal Consta [package insert]. Titusville, NJ; Janssen; January 2019.
439 Geodon [package insert]. Morris Plains, NJ; Pfizer; November 2018.
440 Nuplazid [package insert]. San Diego, CA; Acadia; March 2019.
441 DRUGDEX System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed April 26, 2019.
442 Aristada Initio [package insert]. Waltham, MA; Alkermes; June 2018.
443 Abilify Mycite [package insert]. Rockville, MD; Otsuka; November 2017.
444 Spearing M, Post RM, Leverich GS, et al. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): The CGI-BP. Psychiatry Res. 1997; 73: 159–171.
445 Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960; 23: 56-62.
446 Montgomery SA, Asberg M. A new depression scale designed to be sensitive to changes. Br J Psychiatry. 1979; 134: 382-389.
447 Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry. 1978; 133: 429-435.

448 Vieta E, Bourin M, Sanchez R, et al; on behalf of the Aripiprazole Study Group. Effectiveness of aripiprazole v. haloperidol in acute bipolar mania: double-blind, randomised, comparative 12-week trial. Br J Psychiatry. 2005; 187: 235-242.
449 Abilify [package insert]. Rockville, MD; Otsuka; February 2018.
450 Findling RL, Nyilas M, Forbes RA, et al. Acute treatment of pediatric bipolar I disorder, manic or mixed episode, with aripiprazole: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2009; 70(10): 1441-1451.
451 Saphris [package insert]. Irvine, CA; Allergan; February 2017.
452 McIntyre RS, Cohen M, Zhao J, et al. Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. J Affect Disord. 2010; 122(1-2): 27-38.
453 McIntyre RS, Cohen M, Zhao J, et al. A 3-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states. Bipolar Disord. 2009; 11(7): 673-686.
454 McIntyre RS, Cohen M, Zhao J, et al. Asenapine versus olanzapine in acute mania: a double-blind extension study. Bipolar Disord. 2009; 11(8): 815-826.
455 Saphris [package insert]. Irvine, CA; Allergan; February 2017.
456 Saphris [package insert]. Irvine, CA; Allergan; February 2017.
457 Adasuve [package insert]. Mountain View, CA; Alexza; August 2017.
458 Tohen M, Goldberg JF, Gonzalez-Pinto A AM, et al. A 12-week, double-blind comparison of olanzapine vs. haloperidol in the treatment of acute mania. Arch Gen Psychiatry. 2003; 60: 1218-1226.
459 Zyprexa [package insert]. Indianapolis, IN; Lilly; March 2018.
460 McIntyre RS, Brecher M, Paulsson B, et al. Quetiapine or haloperidol as monotherapy for bipolar mania – a 12-week, double-blind, randomised, parallel-group, placebo-controlled trial. Eur Neuropsychopharmacol. 2005; 15: 573-585.
461 Seroquel XR [package insert]. Wilmington, DE; AstraZeneca; November 2018.
462 Seroquel [package insert]. Wilmington, DE; AstraZeneca; November 2018.
463 Pathak S, Findling RL, et al. Efficacy and safety of quetiapine in children and adolescents with mania associated with bipolar I disorder: a 3-week, double-blind, placebo-controlled trial. J Child Psychiatry. 2013; 74(1); e100-109. DOI: 10.4088/JCP.11m07424.
464 Seroquel XR [package insert]. Wilmington, DE; AstraZeneca; November 2018.
465 Smulevich AB, Khanna S, Eerdekens M, et al. Acute and continuation risperidone monotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week double-blind trial of risperidone and haloperidol. Eur Neuropsychopharmacol. 2005; 15: 75-84.
466 Haas M, Delbello MP, Pandina G, et al. Risperidone for the treatment of acute mania in children and adolescents with bipolar disorder: a randomized, double-blind, placebo-controlled study. Bipolar Disord. 2009; 11(7) :687-700. DOI: 10.1111/j.1399-5618.2009.00750.x.
467 Risperdal [package insert]. Titusville, NJ; Janssen; January 2019.
468 Geodon [package insert]. Morris Plains, NJ; Pfizer; November 2018.
469 Latuda [package insert]. Marlborough, MA; Sunovion; March 2018.
470 Latuda [package insert]. Marlborough, MA; Sunovion; March 2018.
471 Latuda [package insert]. Marlborough, MA; Sunovion; March 2018.
472 DelBello MP, Goldman R, Phillips D, et al. Efficacy and safety of lurasidone in children and adolescents with bipolar I depression: a double-blind, placebo-controlled study. J Am Acad Child Adolesc Psychiatry. 2017;56(12):1015-1025. DOI: 10.1016/j.jaac.2017.10.006.
473 Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry. 2003; 60: 1079-1088.
474 Shi L, Namjoshi MA, Swindle R, et al. Effects of olanzapine alone and olanzapine/fluoxetine combination on health-related quality of life in patients with bipolar depression: secondary analyses of a double-blind, placebo-controlled, randomized clinical trial. Clin Ther. 2004; 26: 125-134.
475 Symbyax [package insert]. Indianapolis, IN; Lilly; March 2018.
476 Seroquel [package insert]. Wilmington, DE; AstraZeneca; November 2018.
477 Seroquel XR [package insert]. Wilmington, DE; AstraZeneca; November 2018.
478 Suppes T, Datto C, Minkwitz M, et al. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. J Affect Disord. 2010; 121(1-2): 106-115.
479 Abilify [package insert]. Rockville, MD; Otsuka; February 2018.
480 Abilify [package insert]. Rockville, MD; Otsuka; February 2018.
481 Saphris [package insert]. Irvine, CA; Allergan; February 2017.
482 Szegedi A, Durgam S, Mackle M, et al. Randomized, double-blind, placebo-controlled trial of asenapine maintenance therapy in adults with an acute manic or mixed episode associated with bipolar I disorder. Am J Psychiatry. 2018;175(1):71-79. DOI: 10.1176/appi.ajp.2017.16040419.
483 Zyprexa [package insert]. Indianapolis, IN; Lilly; March 2018.
484 Seroquel [package insert]. Wilmington, DE; AstraZeneca; November 2018.
485 Seroquel XR [package insert]. Wilmington, DE; AstraZeneca; November 2018.
486 Geodon [package insert]. Morris Plains, NJ; Pfizer; November 2018.
487 Bowden CL, Vieta E, Ice KS, et al. Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind trial. J Clin Psychiatry. 2010; 71(2): 130-137.
488 Shadlack KJ, Hennen J, Magee C, et al. Brief reports: A comparison of the aberrant behavior checklist and the GAF among adults with mental retardation and mental illness. Psychiatr Serv. 2005; 56: 484-486.
489 Rojahn J, Helsel WJ. The aberrant behavior checklist with children and adolescents with dual diagnosis. J Aut Dev Dis. 1991; 21: 17-28.
490 Schopler E, Reichler RJ, DeVellis RF, et al. Toward objective classification of childhood autism: Childhood Autism Rating Scale (CARS). J Aut Dev Dis. 1980; 10: 91-103.
491 Aman MG, Tasse MJ, Rojahn J, et al. The Nisonger CBRF: a child behavior rating form for children with developmental disabilities. Res Dev Disabil. 1996; 17: 41-57.
492 Abilify [package insert]. Rockville, MD; Otsuka; February 2018.
493 Marcus RN, Owen R, Kamen L, et al. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. J Am Acad Child Adolesc Psychiatry. 2009; 48(11): 1110-1119.

494 Risperdal [package insert]. Titusville, NJ; Janssen; January 2019.
495 McCracken JT, McGough J, Shah B, et al. Risperidone in children with autism and serious behavioral problems. N Engl J Med. 2002; 347: 314-21.
496 Risperdal [package insert]. Titusville, NJ; Janssen; January 2019.
497 Available at: http://www.biomedcentral.com/1471-244X/7/7#. Accessed April 26, 2019.
498 Montgomery SA, Asberg M. A new depression scale designed to be sensitive to changes. Br J Psychiatry. 1979; 134: 382-389.
499 Rush AJ, Trivedi MH, Ibrahim HM. The 15-item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR: a psychometric evaluation in patients with chronic major depression. Biol Psychiatry; 2003;: 54(5): 573-583.
500 Abilify [package insert]. Rockville, MD; Otsuka; February 2018.
501 Marcus RN, McQuade RD, Carson WH, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol. 2008; 28: 156-165.
502 Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2007; 68: 843-853.
503 Rexulti [package insert]. Rockville, MD; Otsuka; February 2018.
504 Thase ME, Youakim JM, Skuban A, et al. Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: a phase3, randomized, placebo-controlled study in patients with inadequate response to antidepressants. J Clin Psychiatry 2015; 76(9): 1224-1231. DOI: 10.4088JCP/.14m09688.
505 Thase ME, Corya SA, Osuntokun O, et al. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. J Clin Psychiatry. 2007; 68(2): 224-236.
506 Seroquel XR [package insert]. Wilmington, DE; AstraZeneca; November 2018.
507 Bauer M, EL-Khalili N, Datto C, et al. A pooled analysis of two randomized placebo-controlled studies of extended release quetiapine fumarate adjunctive to antidepressant therapy in patients with major depressive disorder. J Affect Disord. 2010; 127(1-3); 19-30.
508 Geddes J, Freemantle N, Harrison P, et al. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. BMJ. 2000; 321: 1371-1376.
509 Geddes J, Freemantle N, Harrison P, et al. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. BMJ. 2000; 321: 1371-1376.
510 Available at: http://www.biomedcentral.com/1471-244X/7/7#. Accessed April 26, 2019.
511 Popp DW, Cohen EA et al. NSA-16 Revisited: Identifying Latent Factors of Negative Symptoms in Schizophrenia. MedAvante. Available at: http://www.medavante.com/wp-content/uploads/2015/07/nsa-16_revisitedef58bbc10e6e6cf4a23fff0000ac3285.pdf. Accessed April 26, 2019.
512 KroenkeK, Spitzer R, Williams J. The PHQ-9. J Gen Intern Med. 2001; 16(9): 606-613.
513 Andreasen NC. Negative symptoms in schizophrenia. Arch Gen Psychiatry. 1982; 39: 784-788.
514 Andreasen NC. The Scale for the Assessment of Positive Symptoms (SAPS). Iowa City, Iowa. University of Iowa Press. 1983.
515 Putzhammer A, Perfahl M, Pfeiff L, et al. Correlation of subjective well-being in schizophrenic patients with gait parameters, expert-rated motor disturbances, and psychopathological status. Pharmacopsychiatry. 2005; 38: 132-138.
516 Duggleby W, Lander J. Cognitive status and postoperative pain: Older adults. J Pain Symptom Manage. 1994; 9: 19-27.
517 Williams J, Holleman D, Simel D. Measuring shoulder pain with the shoulder pain and disability index. J Rheumatol. 1995; 22: 727-732.
518 Valvano M, Leffler S. Comparison of bupivacaine and lidocaine/bupivacaine for local anesthesia/digital nerve block. Ann Emerg Med. 1996; 27: 490-492.
519 Worrel JA, Marken PA, Backman SE, et al. Atypical antipsychotic agents: A critical review. Am J Health-Syst Pharm. 2000; 57: 238-258.
520 Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry. 1988; 45(9): 789-796.
521 Hirsch SR, Kissling W, Bäuml J, et al. A 28-week comparison of ziprasidone and haloperidol in outpatients with stable schizophrenia. J Clin Psychiatry. 2002; 63(6): 516-523.
522 Kane JM, Khanna S, Rajadhyaksha S, et al. Efficacy and tolerability of ziprasidone in patients with treatment-resistant schizophrenia. Int Clin Psychopharmacol. 2006; 21(1): 21-28.
523 Rosenheck R, Perlick D, Bingham S, et al. Effectiveness and cost of olanzapine and haloperidol in the treatment of schizophrenia: a randomized controlled trial. JAMA. 2003; 290(20): 2693-2702.
524 Revicki DA, Genduso LA, Hamilton SH, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and other psychotic disorders: quality of life and clinical outcomes of a randomized clinical trial. Qual Life Res. 1999; 8(5): 417-426.
525 Möller HJ, Riedel M, Jäger M, et al. Short-term treatment with risperidone or haloperidol in first-episode schizophrenia: 8-week results of a randomized controlled trial within the German Research Network on Schizophrenia. Int J Neuropsychopharmacol. 2008; 11(7): 985-997.
526 Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry. 1994; 151(6): 825-835.
527 Vieta E, Bourin M, Sanchez R, et al. Effectiveness of aripiprazole vs. haloperidol in acute bipolar mania: double-blind, randomised, comparative 12-week trial. Br J Psychiatry. 2005; 187: 235-242.
528 Kane JM, Meltzer HY, Carson WH Jr, et al. Aripiprazole for treatment-resistant schizophrenia: results of a multicenter, randomized, double-blind, comparison study versus perphenazine. J Clin Psychiatry. 2007; 68(2): 213-223.
529 Young AH, Oren DA, Lowy A, et al. Aripiprazole monotherapy in acute mania: 12-week randomised placebo- and haloperidol-controlled study. Br J Psychiatry. 2009; 194(1): 40-48.
530 Möller HJ, Riedel M, Jäger M, et al. Short-term treatment with risperidone or haloperidol in first-episode schizophrenia: 8-week results of a randomized controlled trial within the German Research Network on Schizophrenia. Int J Neuropsychopharmacol. 2008; 11(7): 985-997.
531 Lieberman JA, Tollefson G, Tohen M, et al. Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol. Am J Psychiatry. 2003; 160(8): 1396-1404.
532 Smulevich AB, Khanna S, Eerdekens M, et al. Acute and continuation risperidone monotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week double-blind trial of risperidone and haloperidol. Eur Neuropsychopharmacol. 2005; 15(1): 75-84.
533 Emsley RA. Risperidone in the treatment of first-episode psychotic patients: a double-blind multicenter study. Risperidone Working Group. Schizophr Bull. 1999; 25(4): 721-729.

534 Tariot PN, Schneider L, Katz IR, et al. Quetiapine treatment of psychosis associated with dementia: a double-blind, randomized, placebo-controlled clinical trial. Am J Geriatr Psychiatry. 2006; 14(9): 767-776.
535 McIntyre RS, Brecher M, Paulsson B, et al. Quetiapine or haloperidol as monotherapy for bipolar mania--a 12-week, double-blind, randomised, parallel-group, placebo-controlled trial. Eur Neuropsychopharmacol. 2005; 15(5): 573-585.
536 Emsley RA, Raniwalla J, Bailey PJ, et al. A comparison of the effects of quetiapine ('Seroquel') and haloperidol in schizophrenic patients with a history of and a demonstrated, partial response to conventional antipsychotic treatment. PRIZE Study Group. Int Clin Psychopharmacol. 2000; 15(3): 121-131.
537 Schooler N, Rabinowitz J, Davidson M, et al. Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. Am J Psychiatry. 2005; 162(5): 947-953.
538 Lieberman JA, Phillips M, Gu H, et al. Atypical and conventional antipsychotic drugs in treatment-naive first-episode schizophrenia: a 52-week randomized trial of clozapine vs. chlorpromazine. Neuropsychopharmacology. 2003; 28(5): 995-1003.
539 Lieberman JA, Phillips M, Gu H, et al. Atypical and conventional antipsychotic drugs in treatment-naive first-episode schizophrenia: a 52-week randomized trial of clozapine vs. chlorpromazine. Neuropsychopharmacology. 2003; 28(5): 995-1003.
540 Schooler N, Rabinowitz J, Davidson M, et al. Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. Am J Psychiatry. 2005; 162(5): 947-953.
541 Harvey PD, Rabinowitz J, Eerdekens M, et al. Treatment of cognitive impairment in early psychosis: a comparison of risperidone and haloperidol in a large long-term trial. Am J Psychiatry. 2005; 162(10): 1888-1895.
542 Revicki DA, Genduso LA, Hamilton SH, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and other psychotic disorders: quality of life and clinical outcomes of a randomized clinical trial. Qual Life Res. 1999; 8(5): 417-426.
543 Keefe RS, Seidman LJ, Christensen BK, et al. Long-term neurocognitive effects of olanzapine or low-dose haloperidol in first-episode psychosis. Biol Psychiatry. 2006; 59(2): 97-105.
544 Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005; 353: 1209-1223.
545 Adasuve [package insert]. Mountain View, CA; Alexza; August 2017.
546 Potkin SG, Saha AR, Kujawa MJ, et al. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs. placebo in patients With schizophrenia and schizoaffective disorder. Arch Gen Psychiatry. 2003; 60: 681-690.
547 Abilify [package insert]. Rockville, MD; Otsuka; February 2018.
548 Sanford M, Keating GM. Aripiprazole: in adolescents with schizophrenia. Paediatr Drugs. 2007; 9: 419-423.
549 Correll CU, Kohegyi E, Zhao C, et al. Oral Aripiprazole as maintenance treatment in adolescent schizophrenia: results from a 52-week, randomized, placebo-controlled withdrawal study. J Am Acad Child Adolesc Psychiatry. 2017;56(9):784-792. DOI: 10.1016/j.jaac.2017.06.013.
550 Buchanan RW, Panagides J, et al. Asenapine versus olanzapine in people with persistent negative symptoms of schizophrenia. J Clin Psychopharmacol. 2012; 32: 36-45.
551 Rexulti [package insert]. Rockville, MD; Otsuka; February 2018.
552 Correll CU, Skuban A, Ouyang J, et al. Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: a 6-week randomized, double-blind, placebo-controlled trial. Am J Psychiatry. 2015; 172(9): 870-880. DOI: 10.117+/appi.ajp.2015.14101275.
553 Rexulti [package insert]. Rockville, MD; Otsuka; February 2018.
554 Vraylar [package insert]. Irvine, CA; Allergan; November 2018.
555 Durgam S, Starace A, Li D, et al. An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: a phase II, randomized clinical trial. Schizphr Res. 2014;152(2-3):450-7. DOI: 10.1016/j.schres.2013.
556 Kane JM, Zukin S, Wang Y, et al. Efficacy and safety of cariprazine and acute exacerbation of schizophrenia: results from an international, phase III clinical trial. J Clin Psychopharmacol. 2015; 35(4): 367-373. DOI: 10.1097/JCP.0000000000000346.
557 Durgam S, Cutler AJ, Lu K, et al. Cariprazine in acute exacerbation of schizophrenia: a fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial. J Clin Psychiatry. 2015; 76(12): e1574-e1582. DOI: 10.4088/JCP.15m09997.
558 Vraylar [package insert]. Irvine, CA; Allergan; November 2018.
559 Durgam S, Earley W, Li R, et al. Long-term cariprazine treatment for the prevention of relapse in patients with schizophrenia: A randomized, double-blind, placebo-controlled trial. Schizophr Res. 2016;176(2-3):264-271. DOI: 10.1016/j.schres.2016.06.030.
560 Bitter I, Dossenbach MR, Brook S, et al. Olanzapine versus clozapine in treatment-resistant or treatment-intolerant schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2004; 28: 173-180.
561 Naber D, Riedel M, Klimke A, et al. Randomized double blind comparison of olanzapine vs. clozapine on subjective well-being and clinical outcome in patients with schizophrenia. Acta Psychiatr Scand. 2005; 111: 106-115.
562 Cutler AJ, Kalali AH, Weiden PJ, et al. Four-week, double-blind, placebo- and ziprasidone-controlled trial of iloperidone in patients with acute exacerbations of schizophrenia. J Clin Psychopharmacol. 2008; 28(2 Suppl 1): S20-28.
563 Fanapt [package insert]. Washington, DC; Vanda; February 2017.
564 Fanapt [package insert]. Washington, DC; Vanda; February 2017.
565 Loebel A, Cucchiaro J, Xu, J, et al. Effectiveness of lurasidone vs. quetiapine XR for relapse prevention in schizophrenia: A 12-month, double-blind, noninferiority study. Schizophr Res. 2013; 147: 95-102.
566 Harvey PD, Siu CO, Hsu J, et al. Effect of lurasidone on neurocognitive performance in patients with schizophrenia: a short-term placebo- and active-controlled study followed by a 6-month double-blind extension. Eur Neuropsychopharmacol. 2013; 23(11): 1373-1382. DOI: 10.1016/j.euroneuro.2013.08.003.
567 Harvey PD, Sui CO, Oqasa M, Loebel A. Effect of lurasidone on cognition in patients with schizophrenia: post-hoc analysis of a long-term, double-blind continuation study. Schizophr Res. 2015; 166(1-3): 334-338. DOI: 10.1016/j.schres2015.06.008.
568 Citrome L, Cucchiaro J, Sarma K, et al. Long-term safety and tolerability of lurasidone in schizophrenia: a 12-month, double-blind, active-controlled study. Int Clin Psychopharmacology. 2012; 27: 165-176.
569 Latuda [package insert]. Marlborough, MA; Sunovion; March 2018.
570 Sikich L, Frazier JA, McClellan J, et al. Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizo-affective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (TEOSS) study. Am J Psychiatry. 2008; 165(11): 1420-1431.

571 Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005; 353: 1209-1223.
572 Essock SM, Covel NH, Davis SM, et al. Effectiveness of switching antipsychotic medications. Am J Psychiatry. 2006; 163: 2090-2095.
573 Swartz MS, Perkins DO, Stroup TS, et al. Effects of antipsychotic medications on psychosocial functioning in patients with chronic schizophrenia: findings from the NIMH CATIE study. Am J Psychiatry. 2007; 164(3): 428-436.
574 Keefe RS, Bilder RM, Davis SM, et al. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. Arch Gen Psychiatry. 2007; 64(6): 633-647.
575 Stroup TS, Lieberman JA, McEvoy JP, et al. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. Am J Psychiatry. 2006; 163: 611-622.
576 Stroup TS, Lieberman JA, McEvoy JP, et al. Effectiveness of olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia after discontinuing perphenazine: a CATIE study. Am J Psychiatry. 2007; 164(3): 415-427.
577 Caroff SN, Davis VG, Miller del D, et al. Treatment outcomes of patients with tardive dyskinesia and chronic schizophrenia. J Clin Psychiatry. 2011; 72(3): 295-303.
578 McEvoy JP, Lieberman JA, Stroup TS, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry. 2006; 163(4): 563-565.
579 Tran PV, Hamilton SH, Kuntz AJ, et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. J Clin Psychopharmacol. 1997; 17: 407-418.
580 Edgell ET, Andersen SW, Johnstone BM, et al. Olanzapine versus risperidone. A prospective comparison of clinical and economic outcomes in schizophrenia. Pharmacoeconomics. 2000; 18: 567-579.
581 Harvey PD, Green MF, McGurk SR, et al. Changes in cognitive functioning with risperidone and olanzapine treatment: a large-scale, double-blind, randomized study. Psychopharmacology (Berl). 2003; 169: 404-411.
582 Conley RR, Mahmoud R. A randomized double-blind study of risperidone and olanzapine in the treatment of schizophrenia or schizoaffective disorder. Am J Psychiatry. 2001; 158: 765-774. Erratum in: Am J Psychiatry. 2001; 158: 1759.
583 Breier A, Berg PH, Thakore JH, et al. Olanzapine versus ziprasidone: results of a 28-week double-blind study in patients with schizophrenia. Am J Psychiatry. 2005; 162: 1879-1887.
584 Grootens KP, van Veelen NM, Peuskens J, et al. Ziprasidone versus olanzapine in recent-onset schizophrenia and schizoaffective disorder: results of an 8-week, double-blind, randomized controlled trial. Schizophr Bull. 2011; 37(2): 352-361.
585 Zyprexa [package insert]. Indianapolis, IN; Lilly; March 2018.
586 Kane J, Canas F, Kramer M, et al. Treatment of schizophrenia with paliperidone extended-release tablets: A 6-week placebo-controlled trial. Schizophr Res. 2007; 90: 147-161.
587 Davidson M, Emsley R, Kramer M, et al. Efficacy, safety and early response of paliperidone extended-release tablets (paliperidone ER): results of a six week, randomized, placebo-controlled study. Schizophr Res. 2007; 93(1-3): 117-130.
588 Marder SR, Kramer M, Ford L, et al. Efficacy and safety of paliperidone extended-release tablets: results of a six-week, randomized, placebo-controlled study. Biol Psychiatry. 2007; 62(12): 1363-1370.
589 Invega [package insert]. Titusville, NJ; Janssen; January 2019.
590 Invega [package insert]. Titusville, NJ; Janssen; January 2019.
591 Singh J, Robb A, Vijapurkar U, et al. A randomized, double-blind study of paliperidone extended-release in treatment of acute schizophrenia in adolescents. Biol Psychiatry. 2011; 70(12): 1179-1187. DOI: 10.1016/j.biopsych.2011.06.021.
592 Zhong KX, Sweitzer DE, Hamer RM, et al. Comparison of quetiapine and risperidone in the treatment of schizophrenia: A randomized, double-blind, flexible-dose, 8-week study. J Clin Psychiatry. 2006; 67: 1093-1103.
593 Moller H, Johnson S, Mateva T, et al. Evaluation of the feasibility of switching from immediate release quetiapine to extended release quetiapine fumarate in stable outpatients with schizophrenia. Int Clin Psychopharmacol. 2008; 23(2): 95-105.
594 Seroquel [package insert]. Wilmington, DE; AstraZeneca; November 2018.
595 Findling RL, McKenna K, et al. Efficacy and safety of quetiapine in adolescents with schizophrenia investigated in a 6-week, double-blind, placebo-controlled trial. J Child Adolesc Psychopharmacol, 2012; 22(5); 327-42. DOI: 10.1089/cap.2011.0092.
596 Addington DE, Pantelis C, Dineen M, et al. Efficacy and tolerability of ziprasidone versus risperidone in patients with acute exacerbation of schizophrenia or schizoaffective disorder: an 8-week, double-blind, multicenter trial. J Clin Psychiatry. 2004; 65: 1624-1633.
597 Addington DE, Labelle A, Kulkarni J, et al. A comparison of ziprasidone and risperidone in the long-term treatment of schizophrenia: a 44-week, double-blind, continuation study. Can J Psychiatry. 2009; 54(1): 46-54.
598 Sacchetti E, Galluzzo A, Valsecchi P, et al. Ziprasidone vs clozapine in schizophrenia patients refractory to multiple antipsychotic treatments: the MOZART study. Schizophr Res. 2009; 113(1): 112-121.
599 Brook S, Walden J, Benattia I, et al. Ziprasidone and haloperidol in the treatment of acute exacerbation of schizophrenia and schizoaffective disorder: comparison of intramuscular and oral formulations in a 6-week, randomized, blinded-assessment study. Psychopharmacology (Berl). 2005; 178(4): 514-523.
600 Invega Sustenna [package insert]. Titusville, NJ; Janssen; January 2019.
601 Risperdal Consta [package insert]. Titusville, NJ; Janssen; January 2019.
602 Abilify Maintena [package insert]. Rockville, MD; Otsuka; March 2018.
603 Abilify Maintena [package insert]. Rockville, MD; Otsuka; March 2018.
604 Kane JM, Sanchez R, et al. Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week, multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2012; 73(5): 617-624. DOI: 10.4088/JCP.11m07530.
605 Calabrese JR, Sanchez R, et al. Efficacy and safety of aripiprazole once-monthly in the maintenance treatment of bipolar I disorder: a double-blind, placebo-controlled, 52-week randomized withdrawal study. J Clin Psych. 2017; 78(3): 324-331. DOI: 10.4088/JCP.16m11201.
606 Meltzer HY, Risinger R, Nasrallah HA, et al. A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. J Clin Psychiatry. 2015;76(8):1085-90. DOI: 10.4088/JCP.14m09741.

607 Meltzer HY, Risinger R, Nasrallah HA, et al. A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. J Clin Psychiatry. 2015; 76(8): 1085-1090. DOI: 10.4088/JCP.14m09741.
608 Chouinard G, Annable L, Campbell W. A randomized clinical trial of haloperidol decanoate and fluphenazine decanoate in the outpatient treatment of schizophrenia. J Clin Psychopharmacol. 1989; 9(4): 247-253.
609 Wistedt B. A comparative trial of haloperidol decanoate and fluphenazine decanoate in chronic schizophrenic patients. Int Clin Psychopharmacol. 1986; 1 Suppl 1: 15-23.
610 Zyprexa Relprevv [package insert]. Indianapolis, IN; Lilly; March 2018.
611 Zyprexa Relprevv [package insert]. Indianapolis, IN; Lilly; March 2018.
612 Kane JM, Detke HC, Naber D, et al. Olanzapine long-acting injection: a 24-week, randomized, double-blind trial of maintenance treatment in patients with schizophrenia. Am J Psychiatry. 2010; 167(2): 181-189.
613 McEvoy JP, Byerly M, et al. Effectiveness of paliperidone palmitate vs haloperidol decanoate for maintenance treatment of schizophrenia: a randomized clinical trial. JAMA. 2014; 311(19): 1978-1987.
614 Alphs, L, Benson, C, et al. Real-world outcomes of paliperidone palmitate compared to daily oral antipsychotic therapy in schizophrenia: a randomized, open-label, review board-blinded 15-month study. J Clin Psychiatry. 2015; 76(5): 554-561. DOI: 10.4088/JCP.14m09584.
615 Invega Trinza [package insert]. Titusville, NJ; Janssen; January 2019.
616 Berwaerts J, Liu Y, Gopal S, et al. Efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo for relapse prevention of schizophrenia: a randomized clinical trial. JAMA Psychiatry. 2015; 72(8): 830-839. DOI: 10.1001/jamapsychiatry.2015.0241.
617 Keks NA, Ingham M, Khan A, et al. Long-acting injectable risperidone v. olanzapine tablets for schizophrenia or schizoaffective disorder. Randomised, controlled, open-label study. Br J Psychiatry. 2007; 191: 131-139.
618 Olivares JM, Rodriguez-Morales A, Diels J, et al. Long-term outcomes in patients with schizophrenia treated with risperidone long-acting injection or oral antipsychotics in Spain: results from the electronic Schizophrenia Treatment Adherence Registry (e-STAR). Eur Psychiatry. 2009; 24(5): 287-296.
619 Rosenheck RA, Krystal JH, Lew R, et al. Long-acting risperidone and oral antipsychotics in unstable schizophrenia. N Engl J Med. 2011; 364(9): 842-851.
620 Subotnik KL, Casaus LR, Ventura J, et al. Long-acting injectable risperidone for relapse prevention and control of breakthrough symptoms after a recent first episode of schizophrenia. A randomized clinical trial. JAMA Psychiatry. 2015;72(8): 822-829. DOI: 10.1001/jamapsychiatry.2015.0270.
621 Risperdal Consta [package insert]. Titusville, NJ; Janssen; January 2019.
622 Risperdal Consta [package insert]. Titusville, NJ; Janssen; January 2019.
623 Perseris [package insert]. North Chesterfield, PA; Indivior; July 2018.
624 Nuplazid [package insert]. San Diego, CA; Acadia; March 2019.
625 Cummings J, Isaacson S, Mills, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. Lancet. 2014; 383(9916): 533-540. DOI: 10.1016/S0140-6736(13)62106-6.
626 Abilify [package insert]. Rockville, MD; Otsuka; February 2018.
627 Scherk H, Pajonk FG, Leucht S. Second-generation antipsychotic agents in the treatment of acute mania: a systematic review and meta-analysis of randomized controlled trials. Arch Gen Psychiatry. 2007; 64(4): 442-455.
628 Smith LA, Cornelius V, Warnock A, et al. Acute bipolar mania: a systematic review and meta-analysis of co-therapy vs. monotherapy. Acta Psychiatr Scand. 2007; 115(1): 12-20.
629 Macritchie K, Geddes JR, Scott J, et al. Valproate for acute mood episodes in bipolar disorder. Cochrane Database Syst Rev. 2003; 1: CD004052.
630 Cameron C, Zummo J, Desai DN, et al. Aripiprazole lauroxil compared with paliperidone palmitate in patients with schizophrenia: an indirect treatment comparison. Value Health. 2017;20(7): 876-885. DOI: 10.1016/j.jval.2017.03.010.
631 Kisely S, Sawyer E, Robinson G, et al. A systematic review and meta-analysis of the effect of depot antipsychotic frequency on compliance and outcome. Schizophr Res. 2015; 166(1-3): 178-186. DOI: 10.1016/j.schres.2015.04.028.
632 Ortiz-Orendain J, Castiello-de Obeso S, Colunga-Lozano LE, et al. Antipsychotic combinations for schizophrenia. Cochrane Database Syst Rev. 2017;6:CD009005. DOI: 10.1002/14651858.CD009005.pub2.
633 Yang CS, Huang H, Zhang LL, et al. Aripiprazole for the treatment of tic disorders in children: a systematic review and meta-analysis. BMC Psychiatry. 2015; 15:179. DOI: 10.1186/s12888-015-0504-z.